Archives of Dermatology and Syphilology

VOLUME 20 NOVEMBER, 1929 NUMBER 5

ERYTHEMA ELEVATUM DIUTINUM

RÔLE OF STREPTOCOCCI, AND RELATIONSHIP TO OTHER RHEUMATIC DERMATOSES *

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It is not our purpose in this communication to revamp the history of erythema elevatum diutinum, brief though it is, for Trimble [1] dealt with it in the ARCHIVES barely three years ago. His report stimulated a recrudescence of case reports [2] before various regional dermatologic societies, but nothing essentially new was added. There has not been a sufficient accumulation of cases as yet to yield data for establishing a well rounded, representative symptom complex and for analyzing the significance of the Bury and Hutchinson forms. From the original description of the condition by Crocker and Williams [3] in 1894, it appears that the English are best acquainted with the disease, and that except for Trimble's formal report just mentioned, none has been made elsewhere, either in American or in Continental literature, although Trimble, in his discussion, expressed the belief that two other cases had been reported in the United States. Indeed, we find but four cases in addition to Crocker's original ones indexed in the *British Journal of Dermatology* up to 1909 [4] and none (under that name at least) in the subsequent literature except Trimble's. We felt at first that the con-

* Submitted for publication, March 28, 1929.

* Read at the Fifty-Second Annual Meeting of the American Dermatological Association, San Francisco and Del Monte, Calif., July 1, 2 and 3, 1929.

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1. Trimble, W. B.: Erythema Elevatum Diutinum: Report of a Case, with Remarks on Its Nosologic Position, Arch. Dermat. & Syph. **13**:383 (March) 1926; ibid. **12**:596 (Oct.) 1925.

2. Willard: Erythema Elevatum Diutinum, abstr., Arch. Dermat. & Syph. **16**:107 (July) 1927. Hasley: Erythema Elevatum Diutinum, abstr., ibid. **16**: 250 (Aug.) 1927. Templeton: A Case of Erythema Elevatum Diutinum, abstr., ibid. **16**:514 (Oct.) 1927.

3. Crocker, H. R., and Williams: Brit. J. Dermat. **6**:1, 1894. Crocker, H. R.: Diseases of the Skin, ed. 3, Philadelphia, P. Blakiston's Son & Company, 1908, p. 143.

4. Williams: Epitomized Index of Dermatological Literature, London, H. K. Lewis & Company, 1910.

dition might be known already on the Continent but that it was regarded in a different light from erythema elevatum diutinum, and passed under a different name; but Bloch, who saw our first patient during his recent visit, did not diagnose the condition as any specific dermatosis. He regarded it as allied to lupus erythematosus. Probably, then, it is likewise rarely seen on the Continent.

Not to recite the full syndrome of erythema elevatum diutinum, there is a consistent note of rheumatism throughout the clinical complex, which, taken in conjunction with certain dermatologic resemblances to erythema multiforme and granuloma annulare, has led to some criticism as to the validity of its position as an entity. Thus, in a generalized toxic state such as rheumatism, it would not be at all surprising that the lesions of erythema multiforme perstans should be expressed on the skin, and in the light of the unknown etiology of granuloma annulare and its more or less "toxic" histology, it would likewise not be a far cry between it and rheumatism.

It has been our good fortune to encounter two cases, both of which were examined histologically, and in one of which a pure culture of *Streptococcus ignavus* was secured. The histology in the two was identical, and so distinctive that we believe it to be of value in further establishing erythema elevatum diutinum as a clinical entity and in completely separating it from granuloma annulare.

REPORT OF CASES

CASE 1.—Gus E., aged 35, a machinist, white, was originally presented for diagnosis before the Philadelphia Dermatological Society by Dr. Edward Corson.[5] The condition was regarded at that time as xanthoma tuberosum because the nodules and plaques were most conspicuous over the knees, malleoli, elbows, ulnar protuberances and knuckles, and exhibited a faint orange hue. They were in the skin, sharply circumscribed, and could be lifted up like a button from the deeper parts. It was stated that the condition began ten months previously on the ankles as a red papule, the other parts becoming involved later. The patient was obviously psychopathic and had obsessions that his dermatosis was a punishment for contracting syphilis. He was never violent, but so talkative and unruly that he could not be tolerated in hospital medical wards. He had received considerable antisyphilitic treatment, but at the time of presentation the Wassermann reaction was negative, and it has remained so on repeated subsequent tests. He complained of numerous previous attacks of "rheumatism," but it appears that the joints had never become markedly reddened or swollen and that he had never been actually confined to his bed. Ten years previously, he had an injury of the head which did not render him unconscious. He also said that the lesions became periodically swollen, and repeated examinations by us since that time show that his contention was correct; at times the lesions appeared as thick plaques, and at others the infiltration completely disappeared, leaving but a glossy, more or less dusky and hyperpigmented overlying skin, or perhaps a hard fibrotic nodule. No final diagnosis was arrived at at this presentation of Dr. Corson's.

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5. Corson, E.: Xanthoma Tuberosum, abstr., Arch. Dermat. & Syph. **10**:231 (Aug.) 1924.

Later, during hospitalization for "acute infectious arthritis," the temperature arose as high as 104 F. The heart was found moderately enlarged and showed a mild mitral regurgitation. The systolic blood pressure was 120 and the diastolic 80. Following typhoid vaccination, the temperature rose to 104 F., followed by disappearance of the dermatitis; but in three weeks there was a recrudescence of the polyarthritis. The Wassermann reaction of the spinal fluid resulted negatively, and the colloidal gold curve was 00000000-0.

Leukocytes were repeatedly found in the urine, and on one occasion granular casts.

In the therapeutic way, the left tonsil was removed (a second operation), and a single dose of mercurochrome-220 soluble administered, in addition to the conventional salicylate medication.

Fig. 1 (case 1).—Small plaques on the knuckles and knees.

Psychiatrically, the patient was hard to classify; he was "probably a psychoneurotic with hypochondriac ideas," according to the records.

He was exhibited a second time, at the meeting of the Atlantic Dermatologic Conference in Philadelphia,[6] in October, 1924. By this time a biopsy had been performed which disclosed "an acute inflammation of blood vessels as shown by polymorphonuclears and granular material around them." Three blood cholesterol determinations measured 130, 180 and 220 mg. per hundred cubic centimeters.

The patient was shown for a third time at the meeting of the American Dermatological Association in Philadelphia,[7] for diagnosis. At this time the

6. Weidman: Xanthoma en tumeurs, abstr., Arch. Dermat. & Syph. **11**:566 (April) 1925.

7. Weidman: Erythema Elevatum Diutinum, abstr., Arch. Dermat. & Syph. **14**:622 (Nov.) 1926.

following additional information was supplied: During nine days in the hospital the temperature had been normal, except for transient elevations to 99 and 99.2 F. The blood urea nitrogen measured 21; uric acid, 3.7, and blood sugar, 72 mg. per hundred cubic centimeters. Additional biopsies had never disclosed xanthoma cells. On the basis of the histologic examination, the process was regarded as a toxic necrosis affecting particularly the tissue adjacent to capillaries in the subpapillary parts, giving them the effect of thick-walled arterioles with necrotic walls. Polymorphonuclears were closely crowded in this position, although sparingly scattered elsewhere in the upper part of the corium. Independent necroses appeared in the subpapillary regions as minute foci which bore some resemblances to Aschoff's nodules and at once brought the rheumatic history into prominence. Dr. Weidman regarded the dermatosis as the cutaneous expression of the patient's rheumatism, just as xanthoma tuberosum had at times a rheumatic basis.

In the discussion which followed the presentation, Dr. Wile and Dr. Sutton advanced the diagnosis of erythema elevatum diutinum, which was concurred in by Dr. A. M. H. Gray of London, although he added that it might be better to regard it as a persistent erythema multiforme as erythema elevatum diutinum occurred particularly in women. Dr. Weidman indicated that it was possible that this case was streptococcic in origin.

Since that time the patient has worked steadily and presents himself for observation frequently. At times the lesions flatten down to mere pigmentary maculoplaques. Of late, the rims of the ears have become heavily thickened, purple and slightly scaly, and one or two purple nodules have appeared on the bridge of the nose. Mentally, he is the same as when originally seen. Although an autogenous vaccine of *Streptococcus ingnavus* was prepared from a lesion on the knuckle, he declines to receive injections or to supply material for blood culture.

Bacteriologic Examination.—Subsequent to the presentations at the society meetings, a nodule over a knuckle was removed with the cautery, the skin surface first being seared to assure asepsis. The nodule was ground with glass, planted on blood plates and in blood bouillon. On plates a pure culture of nonhemolytic streptococci was obtained, the colonies being fairly numerous, and, it is emphasized, quite unassociated with the ordinary cutaneous surface organisms. It is felt, thus, that the precautions taken to insure asepsis when securing the specimen were adequate, and that the bacteriologic results were representative of conditions deeper in the skin. *Streptococcus ignavus* was determined according to the Holman system. As far as we can find, no reports have been made of bacteriologic studies on erythema elevatum diutinum. We find that a streptococcus was isolated from rheumatic nodules (Le Bourdelles[8]), but it could not be further classified because it would not grow in subcultures.

CASE 2.—Martha O., aged 34, white, married, Polish, ironer in a leather factory for thirteen years, presented two different types of lesions. The first type was characteristic for erythema elevatum diutinum. Thus, there were the thick discoidal plaques, easily lifted up from the deeper parts, dusky red with perhaps a brown undertone, distributed mostly over the knuckles. There were a few on the elbows and one on each leg, laterally. The second type of eruption extended over the entire legs from more or less above the patella to the ankle. The superficial veins were, in addition, slightly varicose. The skin was diffusely dusky

8. Le Bourdelles, B.: Bacteriologic Study of Rheumatic Nodules, Soc. de biol. de Lyon. **98**:691 (Feb.) 1928.

brown, with areas of deeper pigmentation from place to place, and on pressure there was a permanent redness which bespoke diffuse hemorrhage. The centers of the pigmented areas were slightly atrophic. On one internal malleolus there was a superficial pigmented plaque which in morphology was intermediate between the pigmentary areas above and the fully developed plaques on the knuckles, and which served to betray the nature of the pigmentary areas (involuted plaques). According to the patient, the lesions began seven months previously with papules on the backs of the hands; lesions on the forearms, elbows, legs and thigh developed subsequently. They progressed slowly, but showed changes from day to day, such as evanescent swellings and vesiculation, according to the patient's statement.

Fig. 2 (case 1).—Thickenings over the tendo achillis and external malleoli.

There were periods of extreme itching at first; later mild itching was reported over the lesions or sometimes pain. Although the patient was a leather ironer, it appears that her knuckles did not come in contact with the leather. She appeared mentally normal but was phlegmatic. All conversations were conducted through a neighbor who acted as an interpreter.

The rheumatic history in the case may date back ten years to a swollen wrist joint; however, other joints were not affected at that time. But the history is clear for arthritis on three subsequent occasions; one occurred two years before presentation, the second one a year before, and the third one at the time of presentation. The left knee was affected on all occasions. The pulse was quick, and the temperature was 102 F. during the last attack. At the first visit the systolic blood pressure was 218 and the diastolic 115.

The ophthalmologist reported "Complete obliterating vascular changes, sight entirely gone in left eye, and failing fast in the right eye. O. D. 6/15, O. S. —."

Laboratory Examination.—The blood cells appeared as follows:

	Aug. 1, 1928	Aug. 10, 1928	Dec. 14, 1928
Red blood cells	3,900,000	4,300,000	3,650,000
Leukocytes	8,400	8,600	7,200
Hemoglobin	72%	69%	69%
Neutrophils	65%	43%	68%
Lymphocytes	23%	47%	30%
Large mononuclears	10%	8%	2%
Eosinophils	2%	2%	

The urea nitrogen measured 39 mg., dextrose 83 mg. and uric acid 39 mg. per hundred cubic centimeters. A roentgenogram of the knee showed swelling of the suprapatellar bursa. The Wassermann reaction of the blood was negative.

Culture was made from an excised plaque of the finger. Although no organisms grew, we still feel that they may have been present; we may have seared the surface too severely preliminary to biopsy, in our attempts to assure asepsis. It must be realized that the margin of safety is very narrow—only a matter of microns—between the skin surface and the disease hotbed, and the heat penetration of the cutting cautery cannot be accurately estimated and controlled.

MICROSCOPIC CHANGES

In case 1, two biopsies were performed, the first from a smaller lesion on a knuckle, and the second from a larger and presumably older one over the ulnar protuberance. One biopsy, on a knuckle, was performed in case 2 for histologic purposes; the second lot of biopsy material was used entirely for cultural purposes.

CASE 1.—*Biopsy.*—The surface of the section was smooth and regular. The stratum corneum was excessively thickened and consisted of dense strata of hyperkeratotic substance—not parakeratotic. The granular layer was prominent, consisting of three or four layers of coarsely granular, conspicuous cells. As to the prickle cell layer, all of its cells were slightly swollen, the prickles were distinct, the intercellular spaces a little broadened and the nuclei somewhat swollen. They were somewhat elongated perpendicularly, and their form merged insensibly with those of the basal layer, which appeared as tall, columnar or spindle-shaped elements with scanty cytoplasms and a strongly stained nucleus. There was thus given a more or less perpendicular striation effect to the epiderm, particularly in its lowest portions. The basement membrane was regular and intact. Interpapillary pegs extended downward to a moderate and uniform distance, and were broadened, more or less fused, but not irregular in shape.

The Corium: The important change here was a round cell infiltration around the blood vessels, together with a marked infiltration and thickening of their walls. Thus, the reticular fibrillae around the capillaries were highly teased as by edema and frequently contained a coarse network that stained of an intense red color with eosin. Indeed, the intensity was equal to that of the collagen bundles and stratum corneum. We felt at first that this material included fibrin, although the typical arrangement into a reticulum with nodal points could not be made out. We now feel certain that it is reticulum in a state of hyaline degeneration.

This perivascular process had the effect of supplying a thick wall to the capillaries. It required most careful study to discriminate between capillaries and

edematous arterioles; in this problem, the presence or absence of elastic tissue served as our best criterion. The lining endothelium of the blood vessels appeared normal. We have searched carefully for signs of swelling, hyperplasia or damage, but without success; neither could we find any thromboses. The lumina, however, were at times entirely occluded evidently as a result of the extreme pressure of the surrounding infiltrate.

The cells concerned in the infiltration were predominantly polymorphonuclears. They were present in goodly or large numbers within the walls of vessels, but it was around them that the greatest numbers occurred. They often extended to such a distance that the infiltration fused with that around an adjacent blood vessel and resulted in yet larger areas. The leukocytes never appeared to be disintegrated, to give the effect that pus had been produced, that is, liquefactive

Fig. 3 (case 1).—Thickenings or plaques over the external malleolus; neurotic excoriations superadded.

enzymes not operative. However, on search, some positions were discovered where the spindle cells were hyperplastic and where their nuclei were pyknotic and deformed as though in a definitely degenerate state, and here the several members of a leukocytic nucleus were frequently found widespread as though they (the nuclei) had disintegrated. Only occasionally could a lymphocyte or an eosinophilic polymorphonuclear be found distributed among the polymorphonuclears.

The foregoing changes were seen in greatest intensity in the subpapillary region; they were present to lesser degree in the papillae and in the walls of blood vessels deep in the corium, indeed they could be seen in these walls even as deeply as the level of the sweat coils. Furthermore, some of the infiltration was to be seen in the glandular interstitial substance itself; otherwise, the sweat glands appeared to be normal. No sebaceous glands were included in these sections.

Biopsy 2.—The section obtained for the second biopsy, evidently from an older and more advanced lesion, showed the same order of changes as those seen in the first section. However, some of the changes were more extreme. Thus, the stratum corneum as well as the epiderm as a whole were much thicker. The walls of the blood vessels were much thicker; the leukocytes were much more closely packed and extended outward to greater distances than in the preceding section. The leukocytic infiltration around the blood vessels had thus proceeded to such a stage that a practically uniform stratum of infiltration extended throughout the entire subpapillary region, and as a result of this, the blood vessels did not stand out as individuals as clearly as in the first biopsy. They appeared as though distributed uniformly throughout a general zone of leukocytic infiltration, instead of being themselves the points of origin of the zone. Likewise the lumina of the blood vessels were much more markedly contracted than before; and yet it was still impossible to find thromboses, although the lining endothelial cells by this time had become markedly hyperplastic and their nuclei swollen.

The most distinctive feature of the entire histologic study was the intensely pink-staining substance in the walls of the blood vessels, occurring as more or less fused clods which extended in an irregular zone more or less around the lumen and perhaps also irregularly outward into the surrounding tissue. With Giemsa's method it stained deeply blue until the section had become so overdifferentiated that the staining elsewhere was almost worthless; under the latter circumstances, the hyaline substance stained a beautiful shell pink. It did not give the amyloid reaction with gentian violet, and retained a strong purple-blue color long after the other elements had faded under the action of the acetic acid. We regard it as a toxic hyaline degeneration, affecting the fibrous tissue around the capillaries. Not every vessel in this section showed this; instead, many of them had only the finely reticular, loose, edematous environment which was described in biopsy 1. The capillaries in the papillae did not show the change at all; for the most part they exhibited nothing more than hyperplasia and swelling of the nuclei of the endothelium.

Von Glahn and Pappenheimer[9] are of the opinion that this hyaline substance represents fibrin, as illustrated by their colored plate, where the substance in question stains blue by the Gram-Weigert method. We also secured this reaction, but submit that it is not specific for fibrin; "some forms of hyaline," as Mallory indicated, also retain the dye by this regressive technic; that is, it is a differential stain but not a specific one. In our materials we were favored by the morphology of the substance, in addition to staining peculiarities; it took the form of collagen bundles and could be traced peripherally into connection with reticulum fibers, just as Mallory has recently demonstrated by silver technic that normal collagen and reticulum are continuous. This advantage was denied to Pappenheimer and von Glahn, for in their color plate the hyaline material is most irregular in form. We learn from this that under acute toxic influences the normal reticulum fibers around cutaneous vessels not only become hyperplastic, but can swell and assume the form of collagen.

The interstitial substance of the sweat glands in this section was most heavily infiltrated with leukocytes of the same character as those already described. The blood vessels at this level had particularly thickened walls, and the masses of leukocytes adjacent to them were especially closely packed. Obviously, the process was operative most severely in the deeper parts, and to a much less extent

9. Von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, Am. J. Path. **2**:249, 1926.

at the tips of the papillae. As to the sweat coils themselves, the only abnormality that could be certainly established was the presence of an occasional hyaline cast, either in the distal portion of a duct or, less definitely, in the lumen of one of the coils.

Neither Gram's nor Giemsa's method brought out any bacteria.

CASE 2.—The histology in this case, with its marked leukocytic perivascular changes, was of the same order as that already described for case 1, and will be further covered in the histologic summary. The grade of change was intermediate between that of the two lesions examined in case 1. There was but scanty toxic hyaline change in the blood vessels; still, it was indubitable.

Summary and Comment on the Microscopic Changes.—The major pathologic changes may be gathered and interpreted under two headings: (1) an acanthosis in the epiderm and (2) an acute toxic periarteritis

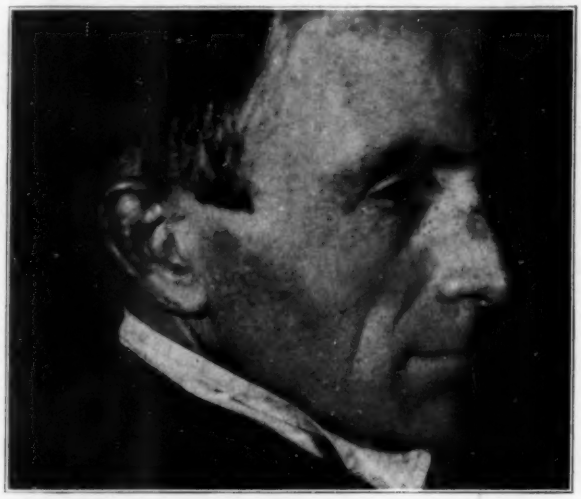

Fig. 4 (case 1).—Infiltration of the rim of the ear and nodules on the nose; these were the latest lesions to develop.

and peritelangiitis in the corium. The acanthosis was not of the most extreme grade possible, being rated as grade II in this laboratory. The excessive thickening of the stratum corneum must be due in greatest part to rubbing on such exposed positions as are concerned in this dermatosis; but, in view of the intensity of the toxic changes observed deeper, we believe that these at least add to the mechanical factors, if there are such in the case, although no infiltration of leukocytes could be seen actually within the epiderm.

As to the acute exudative feature in the corium, this was fully as acute a process as that of erysipelas, but showed damage to the blood vessel walls and, of course, was concentrated around the blood vessels in a much more definite way than in erysipelas. The extremeness of the toxic hyaline change seen in the older lesions is, in our experience, path-

ognomonic, but we must at once emphasize that reliance must not be placed on this alone for the diagnosis of erythema elevatum diutinum. Thus, it will be recalled that in the first biopsy made from an earlier or at least milder lesion, the process had not proceeded thus far, there was but the suggestion of toxic hyaline there. The value of this distinctive toxic hyaline change, therefore, is only positive, that is, if present, it is pathognomonic for erythema elevatum diutinum, but the fact that it is not present is no reason for excluding erythema elevatum diutinum from consideration. There are enough other characteristics to distinguish it.

As far as we know, this is the only dermatosis (of the skin proper) in which masses of polymorphonuclears dominate the picture, apart from such severe acute fulminating conditions as erysipelas and cellulitis and perhaps erythema nodosum.

We doubt that any numbers of bacteria were present in the tissues outside of the vessel walls. They could not be recognized in the Giemsa preparations, and there were no positions where the leukocytes were definitely concentrated or had undergone a particularly high grade of necrosis, such as one would expect to see if there were focalizations of bacteria. And yet it is realized that the micro-organism concerned, *Streptococcus ignavus,* is doubtless one of low virulence and one not calculated to produce microscopic abscesses, so that under the circumstances, while we feel that the tissue changes are more the effect of the toxins of the micro-organisms, it cannot be unequivocally stated that the bacteria themselves are not present in the tissue interstices.

To have three different lots of biopsy material from two different patients is of distinct advantage in the formulation of the scope and limitations to which pathologic changes may take place in this (or any other) dermatosis. As regards erythema elevatum diutinum, a certain grade of acanthosis obtained in all three lesions. The form which this acanthosis took was one in which the interpapillary pegs extended to uniform levels and were not misshapen, and yet they were not quite of the bulbous, graceful type exemplified in psoriasis. While they were broadened they tended to have more or less narrowed lower extremities. The changes around the blood vessels have already been covered in the histologic description of case 2; that is, there was an extreme toxic peritelangiitis, and in addition, a toxic hyaline degeneration of the perivascular collagen which we believe to be pathognomonic. As to the location of the process, whereas it was concentrated particularly in the subpapillary region, it was found extending into the papillae in case 2 (but not in case 1) and extending in intense expression around the sweat glands in case 1, but not in case 2. There thus appears to have been a shift, so to speak, upward in case 2, and downward in case 1; that is, there are possibilities for considerable variation in different cases in respect to the levels which may be attained.

Comparison With Microscopic Changes in Previously Reported Cases.—As far as Crocker's [2] original description went, it readily permitted the inclusion of our case, but he was vague in respect to cytologic details; his illustrations, too, were of the sketchiest type. The lesion "consisted of a fibrocellular structure," but whether the cells were lymphocytes or polymorphonuclears was not mentioned. Neither was toxic hyaline change mentioned, and it is specified that "there was no thickening of the walls." It is possible that it escaped notice, but

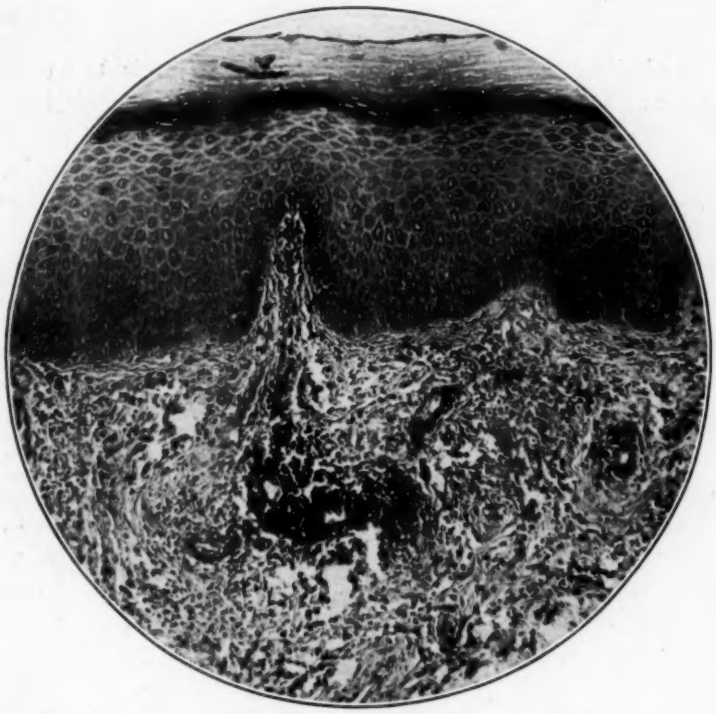

Fig. 5 (case 1).—Section stained by Giemsa. Hyperkeratosis, acanthosis and perivascular leukocytic infiltration. The black material around the vessel represents toxic hyaline, which stained blue-black by this technic. Note that the process extends to the base of the papillae but not to any extent into it.

in view of Trimble's observations we believe that the histology was like his, and represented a later stage than our own cases. Indeed, the only service that the description renders is to show that the process was inflammatory, nonspecific and located deeply in the skin.

The illustrations of Trimble's [1] article did not include any such distinctive features as we illustrate. If they were really representative of the entire lesion, it must have been an old, resolving one, as the stroma is a young fibrous one; still it can be made out that polymorphonuclears

were present. He did not mention polymorphonuclears in his description, and stated that the perivascular infiltrate was only slight. Evidently the entire corium was fibrosed.

Smith's [10] report comprises two lines; "absolutely nothing to be seen except densely matted fibrous tissue; no cells or nuclei could be seen except very occasionally."

The histologic descriptions were thus inadequate for differential diagnosis from closely related dermatoses, and prompted the full report we have given.

PATHOLOGY

It is obvious that erythema elevatum diutinum is the cutaneous expression of a bacteremia; the consistent occurrence of clinical rheumatism reported in it long since is now supported by the demonstration of the micro-organism (*Streptococcus ignavus*) and the distinctive histology. We shall next trace the order of events in its development, beginning at etiology.

To begin with, the pathology of erythema elevatum diutinum is at least that of rheumatism, but only by analogy can we add at once that we feel that it is also that of various other acute infectious conditions. It may lead to better understanding by indicating at once that erythema elevatum diutinum is a syndrome, and comparing it to that other syndrome, erythema nodosum. The latter is generally acknowledged as a syndrome; it is not a specific disease, for whereas rheumatism is commonly at the bottom of it, such other and diversified infections as tuberculosis, anginas, syphilis, spirochetosis, and smallpox seem to have been definitely incriminated. We hear of *Spirochaeta agilis* [11] and tuberculous bacillemias, for instance, in erythema nodosum, albeit the tubercle bacillus does not appear to have been recovered from the blood. In short, it is not to be expected that the same micro-organism will be isolated from every case.

As to the primary excitants of erythema elevatum diutinum, we have no such extensive accumulation of data as in erythema nodosum, and are not prepared to indicate even probabilities at present as to how long the list of agents is. We can, however, speak for rheumatism in the case and indicate the affinities which erythema elevatum diutinum has with other expressions of rheumatism in the skin, or at least peripherally, particularly the morbid anatomy. But it would be backward reasoning to start at erythema elevatum diutinum and develop the thesis thence to rheumatism; it will be far more profitable to outline the full

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10. Smith, F. J.: A Case of So-Called Erythema Elevatum Diutinum, Brit. J. Dermat. **6**:144 (May) 1894.

11. Massini, R.: Spirochaeta agilis in Erythema Nodosum, Schweiz. med. Wchnschr. **51**:739 (Aug. 11) 1921.

scheme of rheumatism so far as it bears on peripheral effects, and view erythema elevatum diutinum only as a part of the panorama, which will include its congener lesions fibrositis, rheumatic nodules and panniculitis. We would appeal to the physician to see etiologically-mindedly; not to become obsessed by refinements or minor variations in degree of morbid change, but to view the scene in its broader aspect—not to miss the forest for the trees. We will pass over such details as the micro-organismal species or filtrable virus, the precise focus of infection,

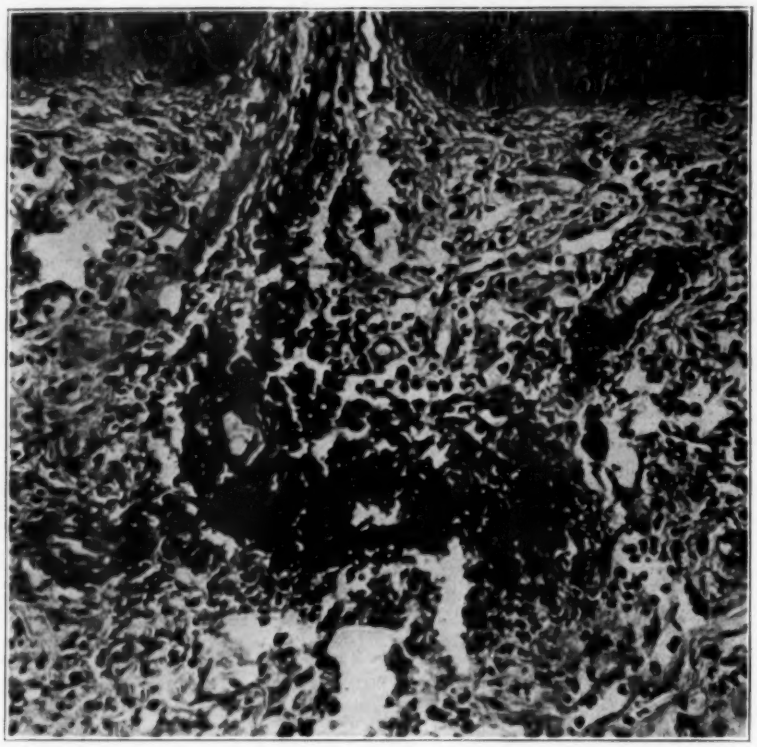

Fig. 6 (case 1).—Higher magnification of figure 5, giving details around vessel, which is probably a capillary arteriole.

bacteremia versus toxemia and the like in rheumatism, which are sufficiently covered in standard works. We will concentrate on the morbid anatomy because we are rather confined to it; through it we will come, in the present state of our knowledge, to the prompter understanding of erythema elevatum diutinum. At the same time, we are mindful of the value which such other features as symptomatology, clinical course, etc., have in establishing the succeeding syndromes. We shall begin at the simplest and more intangible one, namely, fibrositis, and pass thence to the more definite ones.

Fibrositis.—While fibrositis, being deep and diffuse, will scarcely be confounded with erythema elevatum diutinum, it is nevertheless given this place as a lead-off because it is the simplest expression of rheumatism and also probably the commonest. As defined by Edgecombe,[12] who opened a symposium in England on this subject, it is an acute or chronic fibrosis affecting fascias, ligaments, tendons and subcutaneous parts. In the same breath, he mentioned such objects as muscular rheumatism, lumbago, torticollis, cephalodynia, pleurodynia and panniculitis, together with sciatica, brachyalgia and other forms of neuritis. That is, the term is used in a broad clinical sense to indicate subjective symptoms which probably have a rheumatic basis and in which a more or less diffuse fibrosis accompanies the condition. It is thus analogous to arthritis, but translated. Whereas the fibrosis is usually a diffuse one, it appears that at times nodular formation may be associated. In connection with the designation fibrositis the precise causation appears to be a secondary consideration, partly because it is not established, but more probably because there are multiple causes. In fact, some members thought that fibrositis was always infectious, and others that it was often metabolic, assuming connections with gout, diabetes and lead poisoning. It was conceded, however, that rheumatism and also nonarthritic (*viridans*) infections were among the causes of fibrositis.

Edgecombe,[13] in another communication, reported visceral fibrositis affecting the breast, testicles, liver and pancreas. This report was based on the fact that the patients had fibrositis in joints which was readily and unequivocally diagnosable, and had, in addition, symptoms in the aforementioned organs which by analogy were of the same order. No pathologic studies were reported. Although Edgecombe stated that the visceral expressions of fibrositis were rare compared to the peripheral ones, we are inclined to doubt it, for rheumatism is commonly put down as one of the causes of arteriosclerosis; indeed it is generally mentioned in conjunction with diabetes, gout, syphilis and lead poisoning. While chronic interstitial changes in the viscera of rheumatic persons may be difficult to recognize clinically, it is in the nature of things that they must be commonly present where the arteries are so badly compromised.

Histologically, the elements concerned in fibrositis are practically entirely fibrocellular ones; there is little leukocytic infiltration. Bacteriologic examinations almost invariably result negatively.

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12. Various Authors, in discussion on Nature, Prevention, and Treatment of Fibrositis, Proc. Roy. Soc. Med. **19**:21 (Nov.) 1925.

13. Edgecombe, W.: Visceral Fibrositis, Proc. Roy. Soc. Med. **13**:14 (May) 1920.

Gout.—Gout is mentioned largely for the connection it may have with the histologic phase of erythema elevatum diutinum, although some of the English cases of erythema elevatum diutinum show a frank gouty diathesis, and our first patient had lesions on the ears. Of course, the pathology and symptoms of fully developed, classic gout can scarcely be confounded with those of erythema elevatum diutinum or the remainder of the list of related conditions. It is possible, however, that some of the dermatopannicular changes in the acute, infiltrated stages

Fig. 7 (case 1).—Hematoxylin and eosin stain. Transformation of reticular tissue around capillary into collagen-like substance—toxic hyaline; the latter is backed up immediately against the endothelium; clearcut polymorphonuclear infiltration.

of gout would resemble this group histologically, but certainly not in the later stages when the infiltration of uric acid had become established.

Haverhill Disease (Erythema Arthriticum Epidemicum).—An epidemic of Haverhill disease [14] is reported; there were seventy-eight cases

14. Parker, F., and Hudson, N. P.: Erythema Arthriticum Epidemicum, Etiology of Haverhill Fever, Am. J. Path. **2**:357 (Sept.) 1926, illustrated. Jones, L. A., and Lombard, H. L.: Erythema Arthriticum Epidemicum: Investigation of Cases of Unidentified Illness in Haverhill, Mass., Boston M. & S. J. **197**:19 (July 7) 1927.

in thirty-seven families, ten cases occurring in one family. It is essentially an acute general infection, expressed by vomiting, arthritis and an exanthem. The skin changes were morbilliform or scarlatiniform, and affected the arms and legs. The disease is not transmissible from one person to another, but in these cases it was traced to a certain milk supply without quite incriminating it. It was thoroughly studied, *Haverhillia multiformis* (one of the actinomycetales) being isolated eleven times from the blood and twice from joint fluid, which thoroughly established it as the pathogen in the case. Whereas no cutaneous nodules occur in this disease, we cite it because it indicates that the organisms which may produce the rheumatism complex extend into the realm of the fungi.

Rheumatic Nodules.—Rheumatic nodules occur in differing positions according to their size; miliary ones occur in tendons and tendon sheaths; medium-sized ones in broad tendons at joints at insertions, whereas the large ones occur over the bones close under the skin. The seats of predilection are the same as in erythema elevatum diutinum, that is, the elbows, hands, knees and ankles, and after that the head, shoulders, hips, scapulae and clavicles. They are most commonly seen in children, generally in connection with an endocarditis and the severer types of rheumatism accompanied by low fever and prolonged repeated relapses. Chorea not infrequently complicates the disease; it is significant that the foregoing symptom-complex can exist without arthritis, emphasizing once more that we have here again a syndrome referable to different microorganisms, like erythema nodosum, in which the toxemia may or may not affect the joints. The much quoted Aschoff's nodules of the heart are particularly met with in this syndrome. It should be noted in passing that the bacteria are not demonstrable in these rheumatic nodules (exception noted previously in section on bacteriology, case 2); this harmonizes with our observation in erythema elevatum diutinum.

Histologically, rheumatic nodules have the structure of young but compact granulation tissue, highly vascular, and the cells are so closely arranged as to mimic the structure of soft fibroma. There are no polymorphonuclears; in this respect the condition differs from erythema elevatum diutinum. Coates and Coombs [15] believed that there was thrombosis at first, and that fibrosis developed around it subsequently. They pointed particularly at the alimentary tract as the portal of entry, intimating that streptococci of a low grade of virulence were present at all times, ready to invade at the slightest opportunity.

Panniculitis.—The next syndrome to be alined with erythema elevatum diutinum is the "relapsing non-suppurative panniculitis" which is so

15. Coates, V., and Coombs, C. F.: Rheumatic Nodule, Arch. Dis. Childhood **1**:183 (Aug.) 1926.

well known by the English. Weber,[16] who was responsible for arranging this complex, commented concerning the close relationship that there was between it and erythema nodosum. Indeed, in the case reported by Weber and Gray,[17] the only points distinguishing panniculitis from erythema nodosum were the absence of "bruise-like coloration," its extensiveness and poor circumscription.

As to distribution, there seems to be some disagreement among authorities. In Weber and Gray's case, the nodules were present on the extremities, whereas Bain,[18] who saw eighty-six cases in two years, gave as the sites of election the supramammary region, upper intercostal muscles, costal margins, abdomen and the region over the fascia lata. We gather from the reported evidence that transition forms

Figure 8

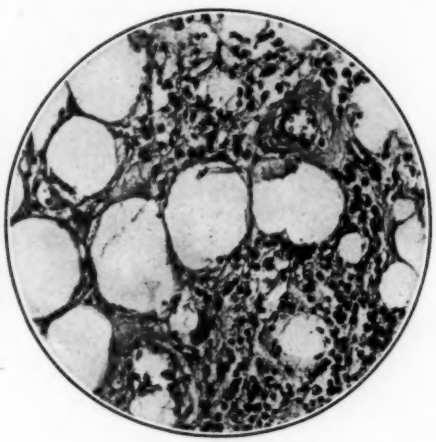

Figure 9

Fig. 8.—Reproduction from Dr. F. Parkes Weber's case of panniculitis, bringing out the polymorphonuclear type of infiltration in this cutaneous expression of rheumatism.

Fig. 9.—Reproduction, illustrating the polymorphonuclear type of infiltration in another rheumatic dermatosis. (Polydermatomysotis.) [17]

between panniculitis, on one hand, and rheumatic nodules and erythema nodosum, on the other, can occur, but that in cases of genuine panniculitis the lesions are usually seen on the trunk, whereas the nodular expres-

16. Weber, F. P.: Case of Relapsing Non-Suppurative Nodular Panniculitis, Showing Phagocytosis of Subcutaneous Fat-Cells by Macrophages, Brit. J. Dermat. **37**:301 (July) 1925, illustrated.

17. Weber, F. P., and Gray, A. M. H.: Chronic Relapsing Polydermatomyositis with Predominant Involvement of Subcutaneous Fat (Panniculitis), Brit. J. Dermat. **36**:544 (Dec.) 1924, illustrated.

18. Bain, W.: Panniculitis, Its Signs and Treatment, Brit. M. J. **1**:450 (March) 1925.

sions are more likely to be seen on the extremities. Weber and Gray discussed thoroughly and clearly the pathogenesis of panniculitis; it is of the same order as that of erythema nodosum. The morbid changes are similar to erythema elevatum diutinum, as indicated by the beautiful photomicrographs of Weber and Gray's case, that is, numerous polymorphonuclears. Christian [19] has described an American case in which the clinical considerations and pathologic changes were in harmony with what has already been recorded; however, his photomicrographs did not show the acute leukocytic type of reaction—lymphocytes and plasma cells featured it.

Dermatomyositis.—Dermatomyositis, while radically different clinically from erythema elevatum diutinum, has probably a similar pathology, and exhibits the same order of histologic changes. It is probably of infectious causation, the infection being a general one and exhibiting peripheral changes in addition. In the extensive compilation reproduced in Steiner's [20] paper, it is indicated that in the twenty-eight cases analyzed there were twenty-four instances in which there were surface cutaneous changes. It is true that most of the cutaneous changes appear to be far removed from erythema elevatum diutinum, the simple diagnosis of erythema, roseola, erysipelatous eruption, etc., being indicated. In two cases, however, pigmentation and desquamation are specified and in yet another an erythema nodosum-like eruption. The latter case, Senator's, which showed the lesions on the arms, legs and thorax, is an important connecting link between erythema nodosum and dermatomyositis clinically. Histologically, the expressions are preeminently of an acutely inflammatory type, featuring edema and polymorphonuclear infiltration, as in erythema elevatum diutinum.

Erythema Nodosum.—Erythema nodosum, we believe, is of the same order of pathologic change as erythema elevatum diutinum, except for its deeper location and vascularity. The microscopic changes are similar, except in the matter of blood extravasations and vascular dilatations. Perhaps these may be referred to the looser tissue present in the subcutis, which affords less support to the walls of vessels than is the case with the corium. Turning to the clinical side of erythema nodosum, the similarity of the distribution of this lesion to that of erythema elevatum diutinum is at once apparent, as it is symmetrical and affects particularly the extremities.

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19. Christian, H. A.: Relapsing Febrile Nodular Non-Suppurative Panniculitis, Arch. Int. Med. **42**:338 (Sept.) 1928.

20. Steiner, W. R.: Dermatomyositis, with Report of a Case Which Presented a Rare Muscle Anomaly but Once Described in Man, J. Exper. Med. **6**:407, 1903.

Periarteritis Nodosa.—Periarteritis nodosa is a condition which has place particularly with the pathologist (Klotz,[21] Guldner [22]) and has to do with nodules of an acute infectious nature which affect smaller arterioles of muscles, nerves and internal organs. The clinical connections of this autopsy table phenomenon have not been thoroughly worked out, but the original impression that it was referable to syphilis seems to be giving way under closer inquisitiveness to one that streptococci and other organisms producing acute inflammation are causative. Most suggestively, from our standpoint, in one case it occurred in connection with what clinically behaved like dermatomyositis (Rosenblath [23]), but it is rather effectually excluded from the rheumatism series enumerated

Fig. 10 (case 2).—Nodules over the knuckles; biopsy wound replacing one of the nodules.

herewith on account of its predilection for smaller arteries, and exclusion from capillaries; in sections of muscle which we ourselves have studied the capillaries were singularly free of the inflammatory phenomena. The process, however, was identical with what we saw in erythema elevatum diutinum, namely, an infiltration of the entire thickness of the

21. Klotz, O.: Periarteritis Nodosa, J. M. Research **32**:1, 1917.

22. Guldner, E.: Periarteritis Nodosa, Including Occurrence in Domesticated Animals, Virchows Arch. f. path. Anat. **219**:366, 1915.

23. Rosenblath: A Rare Disease of the Smaller Arteries of Muscles and Nerves Which Behaved Clinically Like Dermatomyositis, Ztschr. f. klin. Med. **33**:547, 1897.

arterial wall associated with hyaline necrosis of its more luminal parts. As an indication of how strong the suggestion is to an acute infectious implication in this disease, we would cite that in attempting to reproduce periarteritis nodosa, Klotz chose various strains of streptococci.

In review of the foregoing conditions, we find that the same general theme extends through all of them, there being more or less of an acute febrile reaction, tendency to relapses, arthritis and some morbid expression in the skin or subcutaneous parts. Depending on perhaps the virulence of the particular organism concerned, and certainly in a large part on the particular anatomic part affected, different anatomic expressions may be expected to result, such as erythema elevatum diutinum, erythema nodosum and fibrositis. We do not believe that the attempt should be made to establish an invariable or even frequent association, now of one and now the other, of these anatomic expressions with the remainder of the symptom complex. We believe that in this class of disease, involving diversified syndromes, the pathologically-minded physician will be the one least annoyed and perplexed at the overlapping. It is better to have at all times a grasp of the entire system of interrelationships possible, as in purpura; that is, the power to understand the primary portals of entry possible, the variability possible of virulence of the micro-organism concerned, the various anatomic differences in parts which happen to be elected by the virus, and to understand that now one set of combinations may be expected to occur, and now another.

Internal Medical Significance.—In addition to the bacterial and symptomatic harmony between erythema elevatum diutinum and the rheumatic cardiovascular system which have already been dwelt on, the distinctiveness of the histology of erythema elevatum diutinum makes it possible to aline still further these two diseases, because a similar distinctiveness has been established for the rheumatic lesions of the heart and certain arteries. Aschoff's nodules are located in their fusiform distribution in the ventricle by reason of their perivascular location—alinement with coronary arterioles. According to Aschoff, leukocytes (eosinophilic) are associated with their characteristic cells. The recent papers of Pappenheimer and von Glahn [24] are most comprehensive in the histologic direction and render a distinct service in supplying a histologic basis for the appraisal of rheumatic factors. In one, for instance, they submit thirty-five photomicrographs of rheumatic changes in the heart, aorta and other arterial walls showing ranges in histology between acute leukocytic, necrosing processes and the more chronic fibrosing ones—all from the same patient. This confirms what was already sufficiently established, namely, that erythema elevatum diutinum, rheumatic nodules,

24. Pappenheimer, A. M., and von Glahn, W. C.: Studies in the Pathology of Rheumatic Fever, Am. J. Path. **3**:583 (Nov.) 1927; footnote 9.

panniculitis and fibrositis are all fundamentally the same. They are subacute toxic reactions and the differences in histology between these, as well as between Crocker's and Trimble's on one hand and our cases of erythema elevatum diutinum on the other, are referable to differences in intensity (perhaps only of age) of the process.

In our future patients affected by erythema elevatum diutinum we should picture a bacteriemia, with multiple minute hotbeds of activity

Fig. 11 (case 2).—Acute arthritis of the left knee; diffuse dusky erythema and pigmentation of both legs.

in the heart, aorta and other internal vessels, but in which the hotbeds have spurted peripherally even into the skin and betrayed the invader. Or, on the autopsy table, on recognizing such cutaneous lesions, we will be led to inquire more minutely into the cardiovascular state and be guided accordingly in conducting the finer subsequent laboratory studies.

Having thus reviewed the different grades of lesions developing in the skin in connection with rheumatism, we shall see what niche erythema elevatum diutinum in particular occupies in the life history of rheumatism. We shall first consider the cause. Of the various microorganisms concerned in rheumatism, *Streptococcus ignavus* is the only one thus far incriminated for erythema elevatum diutinum. Second, as to tissue processes involved, it stands in the higher levels of acuteness as a pathologic process, yet without producing actual suppuration. In this respect, it is like erythema nodosum and some cases of panniculitis, and unlike rheumatic nodules. Third, it is sharply confined to the skin proper—unlike fibrositis, panniculitis and other conditions. Fourth, tenderness or pain are not featured; perhaps this is because nerve cells are not involved as commonly quoted for rheumatic nodules and fibrositis, which are painful conditions.

If it will be conducive to greater clearness, we may regard erythema elevatum diutinum as a form of erythema nodosum translated to the skin proper, where the lesions fail to become large and where the condition fails to show vascularity and bruise-like features because the expansion of blood vessels is prevented by the denser tissue. Or, we may envisage a widespread systemic, or perhaps only spotty, infectious arteritis, affecting aorta, mesenteric, coronary and other arteries and on occasion extending to cutaneous ones like periarteritis nodosa.

The localization of the dermatosis at points of pressure, together with the infiltrated vessel walls exhibited histologically, invite speculation along the same lines as in xanthoma tuberosum. Evidently a combination of two factors, trauma and damage, is necessary to produce the lesion, but a remaining question cannot be answered now; that is, does vascular damage develop only in the presence of trauma? Must a locus resistentia minoris be created in the wall before the bacterial toxins suffice to damage it? We believe this to be the case, for the alternative situation would predicate the hypothesis that there was involvement of the entire vascular tree to an extent not sufficient to result in localized lesions until sufficient trauma developed. We doubt that this is the case because there is no evidence, either clinically or histologically, that the "sound" skin is compromised vascularly; at least, not morphologically or to an extent over and above that obtaining in any subacute toxemia, and there should be no difficulty in distinguishing between this last grade of change and that observed in the lesions of erythema elevatum diutinum, which we illustrate.

The toxins once lodged in the perivascular tissues, the edema and the leukocytic exudation easily explain the tumefaction seen clinically in recently formed patches. With chronicity, the fibrous tissue development would explain the hard nodules which we saw in our first patient, and which may represent the formations which have been described as

the Bury type in the literature; at least, so far as the pathology is concerned, the Bury type can be reconciled with the hutchinsonian type. That the other features of the two syndromes can be similarly harmonized remains to be seen. We subscribe to Crocker's original opinion that the lesions he studied were "fibromata," but believe that in our two cases we have happened to choose lesions young enough to indicate the unmodified, primary changes in the case.

Fig. 12 (case 2).—Arthritis of the knee. The localization of pigment into certain areas is brought out.

The faint yellow color observed in our first patient was probably referable to residual blood pigment.

The Mental State.—Our first patient was definitely psychotic; and, whereas the expression was not the conventional chorea, it still links up the joints, brain and streptococcus infection. Indeed, the mental state overshadowed other features in this case, at least socially, and

urgently called for even more radical therapy, if available, than the bacterin therapy we had to offer. It is noteworthy that there should have been mental disease in Willard's case also, which is described in the next paragraph.

The Rôle of Phenobarbital.—The rôle of phenobarbital was brought up in connection with Willard's [25] case, presented before the Pittsburgh Dermatological Society. His patient was an epileptic person who was known to have taken phenobarbital over a period of two years. Some of the members regarded the dermatosis as a phenobarbital eruption; Dr. Guy diagnosed it as rheumatic nodules. But the eruption obviously occurred in plaques, and, as Dr. Guy indicated, there was no real clash between the two (rheumatic nodules and erythema elevatum diutinum). We feel certain that drugs may be eliminated as factors in our two patients. In our first patient, there is no possibility that the drug was taken while he was in the psychopathic wards, and it is certain that there was a period of years during which he had the dermatosis and during which he did not take the drug. However, the point is one which should be kept in mind for future judgment.

Disappearance of Lesions Following Antityphoid Vaccination.—The disappearance of lesions following antityphoid vaccination is mentioned only to call attention to the temporary nature of the improvement in our first case, doubtless a nonspecific foreign protein reaction.

Differential Diagnosis.—The differential diagnosis has centered in the past around granuloma annulare. Speaking for our own cases only, there was no confusion clinically because the lesions were so symmetrical, disposed so definitely at points of pressure, and because they were so highly colored, to say nothing of finer dermatologic features commonly recited. Histologically, likewise, they were unlike the granuloma annulares which have passed through our hands; we subscribe to Pollitzer's sentiments in his discussion of Trimble's [1] paper when he complains of the varying histologic appearances described for granuloma annulare by various authors, and we would add that even the picture given by Hartzell is not a type one. This laboratory owns Hartzell's original material illustrated in his textbook,[26] and it does not compare, except in principle, with other specimens which we have studied first hand. It may be that granuloma annulare has such diversified expressions that they might on occasion extend to erythema elevatum diutinum, but we doubt it. Certainly it would never equal the typical, fully developed case as we know it now, although it might resemble an isolated lesion. Pathologically, erythema elevatum diutinum is pre-

25. Willard (footnote 2, first reference).

26. Hartzell, M. B.: Diseases of the Skin, Philadelphia, J. B. Lippincott Company, 1917, p. 573.

eminently acute (in terms of tissue processes), polymorphonuclears being present, but not necrosis (pus). In granuloma annulare the process varies from subacute to chronic, with fibroblastic proliferation as the predominant reactive expression, and extensive necrosis as the rule.

The foregoing facts concern only the clinical syndrome, not the etiology. We cannot deny that granuloma annulare is caused by *Streptococcus ignavus* or some other toxic agent; indeed, on the basis of our only available tangible evidence, namely, the microscopic changes, we feel that it is. Thus, whereas it is easy to cite analogies among other subacute infections, syphilis for instance, in which there are wide ranges

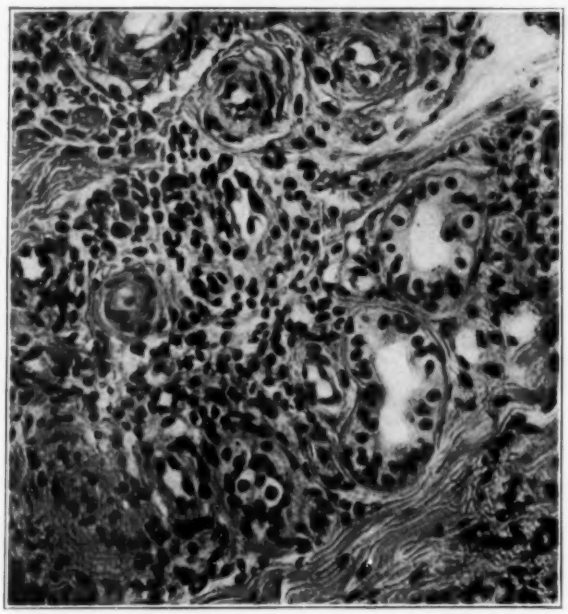

Fig. 13 (case 2).—Position of process even as deeply as the interstitium of the sweat glands; again, polymorphonuclear.

of histologic change producible by the same micro-organism, ordinarily it would be presumptuous to attempt to force granuloma annulare and erythema elevatum diutinum together simply because fibrocellular changes were constantly present in one and sometimes in the other. This is no more than could be said of numerous diversely etiologic entities. But the point is that there is a most distinctive feature—almost pathognomonic—in rheumatic lesions that brings an echo in granuloma annulare, namely, the arrangement of the fibroblastic or endothelioid cells commonly denominated Aschoff cells. Their arrangement in palisades (long dimensions parallel) or radially is well illustrated

by Pappenheimer and von Glahn,[27] and after examination the same theme is readily appreciable and demonstrable in sections of granuloma annulare. The central necrosis frequently seen in rheumatic nodules serves to bring granuloma annulare still further into line with the rheumatic concept. We feel that in the future particular inquiries should be made in re the focal infection—rheumatism—chorea syndrome that may be more or less obscurely present in our cases of granuloma annulare.

As the differential diagnosis of erythema elevatum diutinum from such other dermatoses as sarcoid, lupus vulgaris and xanthoma tuberosum does not involve rheumatic considerations and can be achieved by didactic methods, we shall not be further concerned with this phase of the subject.

All things considered, we believe that sufficient clinical and pathologic criteria can be attached to erythema elevatum diutinum to insure it a position as *a separate entity, both clinically and pathologically, but not etiologically;* but, as with other infectious dermatoses, until the precise micro-organismal etiology is established, for either its individual or its group expressions, there will occur modifications both symptomatically and morphologically to suggest or indicate affinities with other diseases. To avoid confusion, we recommend that for the present the term erythema elevatum diutinum be reserved for the clinical syndrome indicated in the cases of Crocker and of Trimble and in our own cases until a further accumulation of data, particularly etiologic data, may justify revision of the situation.

CONCLUSION

The effects of rheumatism, together with other "focal infectious" states, extend to the skin in the form of other expressions than the widely known rheumatic nodules, that is, Haverhill disease, panniculitis, dermatomyositis, erythema nodosum and erythema elevatum diutinum. In this position the histologic changes are of the same order as those affecting the heart, aorta and other arteries and arterioles, ranging from acute toxic pictures featuring polymorphonuclears to simple fibrocellular changes. Likewise streptococci may be demonstrated in the cutaneous lesions, though rarely.

In addition, some cases of granuloma annulare may have a rheumatic, or at least a "focal infection," basis, as judged from their histologic similarity to certain variants of Aschoff's nodules in the heart and great arteries.

Erythema elevatum diutinum is an entity, distinctive clinically and histologically; it should attract attention to internal infectious states,

27. Pappenheimer and von Glahn (footnote 24, first reference).

first of all, rheumatism; but the possibility that nonrheumatism-producing infections may be also operative should not be denied. When this condition is typical, it is so distinctive that rheumatism can be identified in the case simply on the basis of the cutaneous symptoms, without reference to the medical history in the case. *Streptococcus ignavus* was isolated from one of our cases for the first time in the history of erythema elevatum diutinum, and should be numbered among the primarily exciting organisms; this definitely takes erythema elevatum diutinum out of the erythema multiforme perstans group until or unless it is shown that other noxae can also produce this syndrome.

As new items to be checked against in future cases, we call attention to the mental state, to temporary improvement in the cutaneous lesions under nonspecific foreign protein therapy, as in case 1, and to the development of blindness, as in case 2. As the ophthalmologist independently designated the process as an obliterating vascular one, it is probable that the same order of changes was occurring in the eye as in the skin.

If sufficiently young lesions are available and selected, the histologic picture of erythema elevatum diutinum is pathognomonic, and places it in the short list of dermatoses the histology of which is distinctive per se. Detailed description of the microscopic changes is supplied, being drawn from three biopsies on two patients.

NOTE: While this paper was in press, the communication of Templeton (*Brit. J. Dermat. & Syph.* **40:** 193 [May] 1928) came to our attention. This concerned the case already referred to in footnote 2. The disease was confined to one knuckle, was of the Bury type, and histologic sections gave the picture of granuloma annulare. Dr. Templeton sent us sections from his case, and we confirm his impressions. We are also sympathetic to his hypothesis that, as between granuloma annulare and the Bury form, "the apparently different pathologic picture of these two types may be only different stages of the same underlying process. . . . Central necrosis is possibly caused by the fibrotic process gradually cutting off its own blood-supply, with a resultant destruction of central areas of cells."

ABSTRACT OF DISCUSSION

PROF. JOSEF JADASSOHN, Breslau: The paper of Dr. Weidman is so exhaustive that it is possible to discuss only a few points. I never was able to make the diagnosis of erythema elevatum diutinum, although I saw some cases which recalled to me this disease. The whole group about which Dr. Weidman spoke is difficult to define exactly. We are here obliged to describe exactly the individual cases and to notice the more or less close relationships. I believe that the granuloma annulare is a real entity because the histologic picture is characteristic. I have sometimes seen deeply infiltrated forms and could make the diagnosis only by microscopic examination. During the last years, it seemed to me more

probable than formerly that this disease belongs to the anergic group of tuberculous diseases of the skin. Martenstein found, in my clinic, that the patients he examined in most instances reacted negatively to tuberculin. He found anticutines and procutines, and even lesions of the lungs, as in sarcoids. In the Kiel clinic tubercle bacilli were seen in the tissue, but I believe the cases are not yet frequent enough to give a decision.

Concerning the group of erythema nodosum, I believe that for the present it is advisable to differentiate the cases in which the etiology is known. In other words, differentiate the "secondary" symptomatic group from the group with unknown causes. In the first group known microbes or toxic substances may be the cause; for example, immune bodies, pyemia, tuberculosis, syphilis, gonorrhea, etc., but all of these cases are not really typical clinically. In typical cases we did not find microbes either in the tissue or in the blood, therefore I believe it is probably caused by an unknown specific microbe. The same seems to be true of erythema multiforme, which belongs to the group of dermatoses, very similar to erythema nodosum but not identical, and also to be true of purpura. In our material on erythema nodosum and erythema multiforme, neither the relationship to rheumatism nor to angina seems to be frequent.

I saw a few cases of so-called dermatomyositis, and even one of dermatoneuromyositis. There seem to exist relationships to scleroderma, especially in its acute form. I also saw some cases of atypical erythema induratum without any demonstrable tuberculous infection. These cases are rare and must be studied as Dr. Weidman has studied his case. I want to make note of the fact that the histologic description Dr. Weidman gave reminds one of the description given by E. Fränkel in the metastatic acute dermatosis. When we study all of these cases in this manner, we will be able to see whether in this whole group exist some clinical entities with a specific etiology.

Dr. Weidman, Philadelphia: I wish only to emphasize the care employed in securing the cultures in our first case. Perhaps the reason I did not succeed in the second case was that I overreached in my precautions. In case 1, the material was excised only after deep cauterization of the surface, and the biopsy was made entirely by the use of the cautery knife.

DERMATOLOGY IN BRAZIL*

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NEW YORK

The opportunity recently came to me to visit Brazil under peculiarly favorable conditions from the standpoint of dermatologic study. Dr. de Mello of Syracuse, who originally came from Brazil, recently returned to his native country for a visit, preceding me by a few weeks. This enabled him to make plans for me to give some lectures before medical societies and to meet the leading dermatologists of Brazil. One of my objects was to observe and photograph cases of the Brazilian type of cutaneous leishmaniasis, which I hope to report on later.

It may be of interest to recall the fact that Brazil is larger than the United States and greater in population and area than all the rest of South America. It is composed of twenty states and the federal district of Rio de Janeiro, the latter being also the name of a state. Of the four cities which I visited, Rio de Janeiro or Rio, as it is commonly called, and São Paulo are the largest and most important from medical as well as from other standpoints. The former has nearly 2,000,000 and the latter about 1,000,000 inhabitants. To avoid confusion it should be mentioned that São Paulo is the name of a state as well as of a city. Bahia, the third largest city, has the oldest university in Brazil but is not nearly as progressive as the others. It is picturesque but dirty and its population is composed largely of negroes. Santos is the port for the city of São Paulo and while of importance commercially has little of medical interest.

To my surprise, Dr. William T. Corlett was the only American dermatologist to have visited Brazil within the memory of the men I met. At least he was the only one to have made himself known. My visit was apparently the first one in recent years for purely medical purposes. This may account for the universal kindness and attention that was paid me, though the Brazilians are known to be friendly to Americans and famous for their hospitality. Since Dr. Corlett's visit in 1915, the status of dermatology has changed in Brazil as in other parts of the world. Much of the work of Brazilian dermatologists is not well known to most Americans as their publications appear in Portuguese or in languages other than English. The work of their leading men is of high class and with the new building program of the universities of Rio and São Paulo the opportunities for making great strides are unlimited.

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* Submitted for publication, Oct. 6, 1929.

* Read before the Section of Dermatology and Syphilology, New York Academy of Medicine, Oct. 1, 1929.

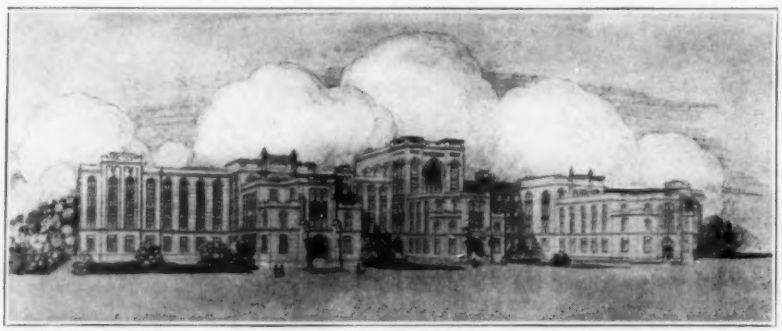
The University of Rio de Janeiro has about 6,000 students, of which about 2,500 are in the schools of medicine, dentistry and pharmacy. The number of medical students is generally admitted to be too large for the present equipment, there being no limitation to the size of entering classes. The course of instruction requires six years. The hospital for teaching purposes is the Santa Casa, a name used for similar institutions in other cities of Brazil. It is a private hospital for charity patients, supported by voluntary contributions, the nurses being Sisters of Charity. It has 1,000 beds.

The Department of Dermatology and Syphilology at the University of Rio is headed by Professor Eduardo Rabello, who has held this position for twenty-three years. Professor Rabello is an excellent organizer and administrator and is the most prominent active dermatologist in Brazil. In addition to being a well informed man, he is universally liked on account of his delightful personality. He has a staff of eighteen men, including his Chief of Clinic, Dr. Oscar da Silva Araujo, and two docents, Dr. Arminio Fraga and Dr. Joaquin Motta, all of whom are active and capable men. Instruction in dermatology and syphilology is given to the sixth year students, six hours a week during the college year (eight months). Lectures are given by Professor Rabello once a week, those on syphilis being didactic. The majority of the lectures are clinical. Other instruction is given to small groups of students by six assistants. The professor and his teaching staff are all paid by the government.

The quarters occupied by the dermatologic department are of moderate size though the equipment is mediocre in some respects. The skin department has no roentgen ray apparatus, the roentgenologic work being centralized in another part of the hospital. It is fortunate, however, in having a large amount of radium for its own use. The outpatient department has an average attendance of seventy or more patients. During my visit to the wards (thirty-eight beds for men), I was delighted to see my first case of ainhum, pronounced "ine-yum," the h being silent in Portuguese. The patient, a negro, presented the characteristic constriction of one little toe, the opposite little toe having been lost previously by spontaneous amputation. I was told that this curious disease was rare at present in both Rio and São Paulo. Having so recently seen my first cases of coccidioidal granuloma on the Pacific Coast, I was interested to see another example of this disease known in Brazil as blastomycosis, although caused by *Coccidioides imitis*. In addition there were three cases of granulomatosis inguinalis and one of typical xeroderma pigmentosum in a man of 60 in whom the disease had first appeared at the age of 12. There were also numerous cases of granuloma inguinale, which, I explained, were familiar to those living in New York.

While the present quarters of the department of dermatology are not unusually large, plans are under way for one of the most completely equipped and largest skin departments to be seen in the world, certainly more impressive than anything we have at present in the United States. The new clinic will consist of an entire wing of a new hospital with six stories, containing 150 beds for adults and children, including accommodations for private patients. Separate rooms are provided for microscopy, bacteriology, serology, mycology, dentistry and social service. Provision is also made for complete physical apparatus, including Finsen and roentgen rays. Each ward is to have a demonstration room for students and there are to be two amphitheaters, a museum and a library. A superintendent is to be assigned to the skin department alone.

A new and elaborate "medical center" is now being built in the progressive city of São Paulo. It is to occupy an area of 300,000



New laboratory building of the medical school in São Paulo.

square meters (74 acres) on high ground overlooking the city. Three buildings are already in operation, including the Hygienic Institute, modeled after similar institutions in Johns Hopkins and Harvard Universities, the Department of Legal Medicine. Altogether there will be ten buildings. The impressive-looking one for the laboratories is now in the process of construction. The plans for this medical center were made after long and careful study, a commission of three members of the faculty having been sent to the United States and Europe by the Rockefeller Foundation to study leading medical schools and hospitals. One of the Commissioners, Dr. Souza Campos, who is professor of bacteriology and also an engineer, showed me the plans and took me through the new buildings. The number of students is at present limited to fifty for the entering class and will be increased later to eighty. It is expected that the new school will serve as a model for Brazil and other South American countries. To help build the school the Rockefeller Foundation contributed $1,000,000.

The department of dermatology and syphilology was for the time being somewhat disorganized owing to the recent resignation of Prof. Adolpho C. Lindenberg. I was disappointed in not seeing Professor Lindenberg, whom I had previously met in New York and later in Germany. He had gone to Europe for a visit. The professorship had been given to Dr. J. de Aguiar Pupo, who had previously held the chair of pharmacology. There had not been sufficient time for him to organize his service nor had any definite plans been made for his department in the new medical school. Prof. Lindenberg had retained his service in the Santa Casa Hospital which I visited daily for a week in order to study leishmaniasis. I was given all possible assistance by Dr. Abilio Martins de Castro and Dr. Nicolau Rossetti, assistants of Professor Lindenberg, both keen and well informed dermatologists. Dr. Martins de Castro was especially interested in laboratory work and was a good mycologist. Among other talents he showed great artistic ability in making drawings of hanging drop cultures.

The dermatologic ward of Professor Lindenberg had thirty-five beds, but was crowded with twice that number of patients, half of them sleeping on mattresses on the floor. This was no hardship for the type of charity patients that I saw. About 70 per cent of patients admitted to this service suffer from cutaneous leishmaniasis. I was able to obtain photographs from seventeen of the fifty cases that I saw. Many showed active ulceration and in some cases considerable deformity of the nose. Involvement of the nasopharynx was estimated to be present in about one third of the cases of leishmaniasis. Some of the lesions of the mucous membrane were demonstrated to me by Dr. Paula Santos, professor of laryngology. In Dr. Lindenberg's ward I also saw another case of coccidioidal granuloma and one case of mycetoma affecting the knee, presenting numerous sinuses suggesting actinomycosis. There was an unusual case of verrucous dermatitis or "mossy foot," caused by a fungus. There were also cases of pemphigus, one of the vegetating and five of the foliaceous type. These types were said to be much more common in Brazil than pemphigus vulgaris.

There are two dermatologic societies in Brazil, an important national one and a local one in the state of Minas. The national society is known as "Sociedad brasileira de dermatología e syphilographía." It has about fifty members scattered over the republic, the majority being in Rio and São Paulo. There is no membership limit. It was founded in 1912 and meets monthly in Rio during nine months of the year. Prof. Rabello is the president. For the first time this year an annual meeting was held in Rio and a similar meeting is planned for São Paulo, the next year. There is no separate dermatologic society in São Paulo, the general medical society in that city being divided into sections. The national society has had its own journal for the past

seventeen years. It is published every three months and contains both transactions and original articles. It was first called *"Boletín"* but is now known as *"Anales brasileiros de dermatologia e syphilographia."* The editor is Dr. Silva Araujo. His father, it may be mentioned, was the most distinguished of the pioneer dermatologists of Brazil. The small society in Minas is known as "Sociedad Mineira de dermatología en Bello Horizonte."

Syphilis and leprosy constitute two of the most important medical problems in Brazil. An estimate by conservative physicians of the prevalence of syphilis in Brazil is about 14 per cent of the entire population. Its incidence is somewhat greater in the large cities. The word syphilis, it may be said, is freely used in polite society and in all lay journals. The effort to control venereal disease is carried out in an intelligent and comprehensive manner. In Rio, this has been made possible through the generosity of two wealthy and public spirited families, who have formed the Gaffreé Guinle Foundation. Working under this foundation there is a branch of the Health Department for venereal diseases and leprosy known as the "Inspectora de profilaxis de lepra e dos dolencias venéreas." This bureau operates as a private charity under the auspices of the federal government. The plan of campaign was originated by Professor Rabello and is being carried out under the direction of its chief, Dr. Silva Araujo. At present there are fifteen dispensaries scattered over the city of Rio for the treatment of venereal diseases. The largest of these accommodates 2,000 patients daily (except Sunday) from 7 a. m. to 9 p. m. During the past year, there was a total of 1,500,000 visits in all the venereal dispensaries. In all of them treatment is free.

The new Gaffreé-Guinle hospital, which will soon be opened, is a model institution with 350 beds and a separate adjoining building with complete laboratory facilities for research in syphilis. There is nothing similar to it in the United States. It might be mentioned that several members of the Guinle family, who now carry on the Gaffreé Guinle Foundation, are as public spirited as they are wealthy. In addition to contributing freely for the fight against venereal disease, one of the family, Señor Guilherme Guinle, has also founded an institute in Rio for cancer research which has a hospital of 150 beds. He has also given money for a large leprosarium with special research facilities, the institution to be built when a suitable site is obtained.

While the routine treatment for syphilis is carried out in all of the dispensaries mentioned, there are special services for prenatal and postnatal cases, for children, for neurologic and for visceral syphilis. The last mentioned is under the charge of an internist, the clinic being equipped with electrocardiographic and roentgen ray apparatus. Neurologic syphilis is under the charge of a neurologist, cases being referred

from other dispensaries. In the past seven years, 4,500 lumbar punctures have been made. At present, however, the cisternal puncture has almost entirely replaced the spinal method, 1,500 cisternal punctures having been made in the last two years. Neoarsphenamine (German) is administered as a routine, always by the syringe method, and during the past eight years in a maximum dosage of 0.6 Gm. This is of interest in view of the recent remarks of Schamber and Jadassohn at Del Monte. About 2,000,000 injections of neoarsphenamine have been given, with two deaths. In one case the patient ate a hearty meal and did some strenuous rowing immediately after treatment. The other death occurred in a hemiplegic patient. Bismuth is used much more frequently than mercury. About 200 patients with tabes and paresis have thus far been treated with inoculations of malaria, and this method is being tried in early neurosyphilis and in Wassermann-fast cases. For the Wassermann test a Brazilian modification of the Sachs method is used. Three colloidal tests are made as a routine (mastic, benzoin and colloidal gold). Experimental work has also been done with the Kahn test.

The prevalence of leprosy in Brazil is shown by the census of last year with 14,322 cases in the entire republic. There were 831 cases in the federal district of Rio alone. Dr. Souza Araujo estimated that in 1924 the actual number of cases was 24,000. There are two principal endemic centers in Brazil, one in the northern equatorial zone (states of Amazonas, Para and Maranhao) and one in the central temperate zone (states of São Paulo and Minas). At present there are eight colonies in addition to small hospitals for lepers. When the diagnosis is made by a member of the Federal Department of Health, the patient may be allowed to remain at home if the living conditions are satisfactory. If the patient is indigent or unwilling to follow instructions he is compelled to go to a leper hospital. Patients may be paroled though this seems to be unusual. A bacteriologic examination is made in every new case though the presence of bacilli is not considered essential for a diagnosis. The majority of cases are of the mixed type. In the northern hot districts a relatively greater proportion of anesthetic cases is seen. Immigrants from Spain, Portugal and Italy usually suffer from the nodular type, these cases constituting about one tenth of all the lepers in Brazil. During the time of slavery leprosy was common in negroes. At present more white persons are affected. According to Dr. Silva Araujo, the disease is less common in mulattoes. Children born of leprous parents are taken from them immediately after birth. In São Paulo there is an asylum for healthy children born of leprous parents. They are kept there till the age of 14. A similar institution is proposed for Rio.

I had the opportunity of visiting a leper hospital in Rio and a leper colony near São Paulo. The "Hospital Dos Lararos" in Rio is a clean and well conducted private institution, aided by the federal government. At present it has about 100 patients, all of them surprisingly cheerful. The leper colony near São Paulo, known as "Asylo Colonia de Santo Angelo," is situated about 30 miles from the city. It is a modern well equipped institution which has been in operation for the past year. At present there are nearly 600 patients, including men, women and children. Special quarters are provided for twenty married couples. There are thirty-seven buildings and others in the process of construction. They are built largely by the patients themselves, who are paid for their work. Various occupations for patients, such as bricklaying, carpentering, sewing, etc., are provided. To aid the morale, there are many forms of recreation, including a radio in every building, a theater, a dramatic association, two brass bands and two soccer football teams, one of them being called the "Hope Club." The nurses are Sisters of Charity, the Sister in charge being unusually intelligent and capable. There are separate schools for boys and for girls. The institution was built by the state of São Paulo, which also pays two thirds of the current expenses. The state government plans to have four other similar colonies, two of which are under construction. If this program is carried out, it is hoped that the disease will be stamped out in the state of São Paulo in a generation. Prof. Aguiar Pupo is the physician-in-chief, his staff consisting of two dermatologists, two internists, one oculist, one bacteriologist and one dentist, in addition to a resident physician.

Brief mention should be made of several other medical institutions of Brazil. The Academia Nacional de Medicina is an exclusive body of 100 physicians meeting weekly in Rio in their own building. Its one-hundredth anniversary was recently celebrated, at which time Dr. Darier was one of the guests. Unfortunately for me he had left just before my arrival. I had the honor of giving an illustrated lecture before the Academy, speaking in French. It was somewhat embarrassing, however, to learn that the speaker who was to precede me was a physician from Paris. Later I had the pleasure of giving another lecture before the dermatologists of Rio. In regard to language, I should say that French is invaluable for conversing with physicians in Brazil. Many speak and practically all understand French, but comparatively few speak either English or German. Ability to speak Spanish fluently would enable an American to talk not only with educated Brazilians, but with the lower classes as well.

The Oswaldo Cruz institute in Rio was founded in 1901 by the man whose name it now bears, and it is similar to the Rockefeller Institute in New York. Of the eight separate departments, that of mycology

was of special dermatologic interest. It is under the charge of Dr. Olympia da Fonseca, Jr., who is also one of Professor Rabello's assistants in the University Clinic. Dr. Fonseca had about 1,200 cultures from 300 different species of fungi. He had been connected with the institute for ten years and was assisted in his work by four physicians and two lay technicians. He was writing a book on mycology, one volume of which is in press. Dr. Fonseca gave me specimens of peidra hairs, though I did not see any patients presenting this curious disease.

At the Institute of Hygiene in Rio, I was told of satisfactory results with the complement fixation test for leprosy using Deycke's antigen (defatted *Streptothrix leprae*). I was given some of this antigen for trial in my clinic. At the Hygienic Institute in São Paulo smears and cultures of *Leishmania braziliensis* were obtained from Dr. Oliveira da Fonseca, a brother of the dermatologist in Rio. He said that the organisms could be obtained in a greater percentage of cases by culture than by smear, but found it extremely difficult to demonstrate them in stained sections. It seemed surprising that Dr. Fonseca could converse fluently in French, German and English, though he had never been away from Brazil.

The nonmedical part of my trip included glimpses of the beautiful scenery of Rio and Santos, a visit to a large coffee plantation and to the famous snake farm (Butantan) of São Paulo. For others who might take a similar trip it should be mentioned that the seasons are reversed in Brazil, our summer being their winter. My visit was therefore delightfully cool, even uncomfortably so at times in São Paulo. The sea voyage on ships, designed for tropical service, occupied twelve days from New York to Rio and a day longer on the return trip. The kindness and hospitality of the Brazilian physicians could not have been exceeded. On my arrival at São Paulo, where I gave my third lecture, before a special meeting of the general medical society, the president, Dr. Schmidt Sarmento, with several others, took the trouble to meet me at the train. Brazilian hospitality included some complimentary remarks in the course of newspaper interviews, one reporter remarking that I was an agreeable "young" man.

In conclusion I should highly recommend a trip to Brazil for my colleagues who desire to see certain tropical skin diseases and who enjoy beautiful scenery and a restful sea voyage. It is high time that we established closer relations with our dermatologic colleagues in Brazil as well as in other Latin American countries. They are as progressive as they are hospitable.

DERMATOSIS PAPULOSA NIGRA*

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AND
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Castellani [1] first named and described dermatosis papulosa nigra in a brief note, and later, in collaboration with Duval,[2] expanded his original clinical report and included a brief pathologic study. For several years this dermatosis has attracted our attention, and during that time we have collected some observations of it which form the basis of this paper. In the main, we have been interested in its incidence, pathologic changes and nosologic position, but before proceeding to these phases of the subject, we shall describe its clinical features as a review and amplification of Castellani's observations.

SYMPTOMATOLOGY AND INCIDENCE

The disorder occurs almost exclusively among negroes; we have seen it once in a Mexican of the peon class, while Castellani saw it in a European. We noted that the disorder may appear in childhood, as early as the seventh year. At this age, minute, round, semiglobular papules, skin colored or more often somewhat more than normally pigmented, develop singly or in sparse numbers on the malar regions or on the cheeks below the eyes. The lesions become larger and more prominent at and beyond the age of puberty and also increase in number. In an average case perhaps from thirty to fifty lesions are present, chiefly on the anterior and lateral surfaces of the upper part of the face, including the eyelids, and occasionally we have noted lesions on the upper part of the back. In fully developed cases, the lesions are rounded, angular or spindle-shaped, always isolated and perceptible at some distance (fig. 1). They are from 1 to several millimeters in their longest diameter, and are raised about 0.5 mm. The surface of the early lesions is smooth, but later they become somewhat wrinkled and cross-hatched. They give hardly any resistance to palpation. They simulate, to a certain extent, the size and shape of verruca plana. They do not itch or

* Submitted for publication, March 25, 1929.

* Read at the Fifty-Second Annual Meeting of the American Dermatological Association, San Francisco and Del Monte, Calif., July, 1929.

* From the Dermatologic Section, Jefferson Davis Hospital.

1. Castellani, A.: Observations on Some Diseases of Central America (Dermatosis Papulosa Nigra), J. Trop. Med. **28**:1 (Jan. 1) 1925.

2. Castellani, A., and Duval, C. W.: Dermatosis Papulosa Nigra, Arch. Dermat. & Syph. **18**:393 (Sept.) 1928.

produce other subjective symptoms. There is no scaling, crusting or ulceration. The lesions seem never to disappear spontaneously.

The incidence of this condition has been determined by examining 2,230 negro children in the public schools of this city and by observation of patients at a negro clinic. We are indebted to the school authorities, especially Dr. T. O. Woolley, chief school physician, for the opportunity to examine the school children.

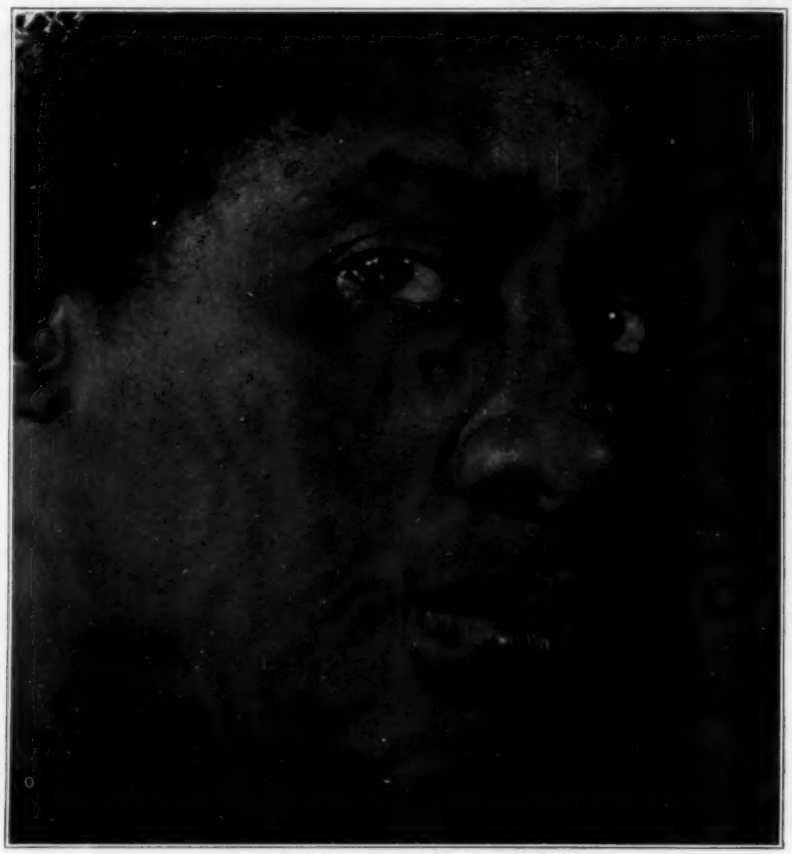

Fig. 1.—A typical case of dermatosis papulosa nigra.

The accompanying table gives a tabulation of our observations. For the purpose of noting whether or not the condition became more pronounced as the age advanced, we divided the cases into mild, definite and pronounced types. It will be seen that the condition in the first group of cases in which the lesions are barely perceptible occurs more commonly during the earlier years, while the definite and pronounced types preponderate among youths and adults. The disorder appears during or just preceding puberty and seems to reach its acme during early adult

life. Our observations reveal a definite sex influence; that is, the condition was found from three to four times more frequently in females than in males, though in the school children examined there were approximately only twice as many females as males. This preponderance of the condition in females in children is also found in adults.

In 198 adult negro patients who presented themselves for treatment, we found nineteen cases (10 per cent) of the definite and pronounced types. Our figures therefore show that the incidence of the dermatosis in the negro race of this section of the country is between 6 and 12 per cent.

From statements of our patients, we have been led to believe that there is a familial tendency to the disturbance, but we are unable to make definite statements on this point, because of the difficulties attendant on the tracking down and examination of entire negro family groups.

Incidence of Disorder in School Children

Age	Number Pupils	Number Positive	Sex		Total Percentage Positive	Mild		Definite		Pronounced	
			M	F		Number	Per Cent	Number	Per Cent	Number	Per Cent
7-11	884	48	12	36	5.4	44	5	3	0.35	1	0.1
12-15	1,148	169	36	133	14.7	118	10.3	42	3.6	9	0.8
16-18	198	47	12	35	23.8	31	15.8	11	5.5	5	2.5
Total	2,230	264	60	204	12	193	8.6	56	2.5	15	0.6

We also noted that the disorder was practically limited to those persons of pure or at least three-fourths negro blood as judged by facial, pigmentary and pilous characteristics. Only one child that was classed as a mulatto presented the dermatosis.

MICROSCOPIC OBSERVATIONS

For histologic study we obtained material from three patients; two were men, aged 49 and 43, respectively, and one was a woman, aged 60. The lesions removed were clinically typical. All were from the upper part of the face.

The specimens were embedded in paraffin and stained with hematoxylin-eosin and Weigert's elastic tissue stain.

Epidermal changes are the most pronounced feature. Serial sections showed that the earliest change peripherally was slight acanthosis with down-growth and broadening of the rete pegs (fig. 2). The corneus and granular layers presented no noteworthy change in any of the sections. The basal layer was either irregularly or uniformly hyperpigmented; the pigment (apparently melanin) being dense enough to mask completely the cells or else occupying the cytoplasm as a nuclear cap (fig. 3). Not only was the basal layer pigmented, but in those areas

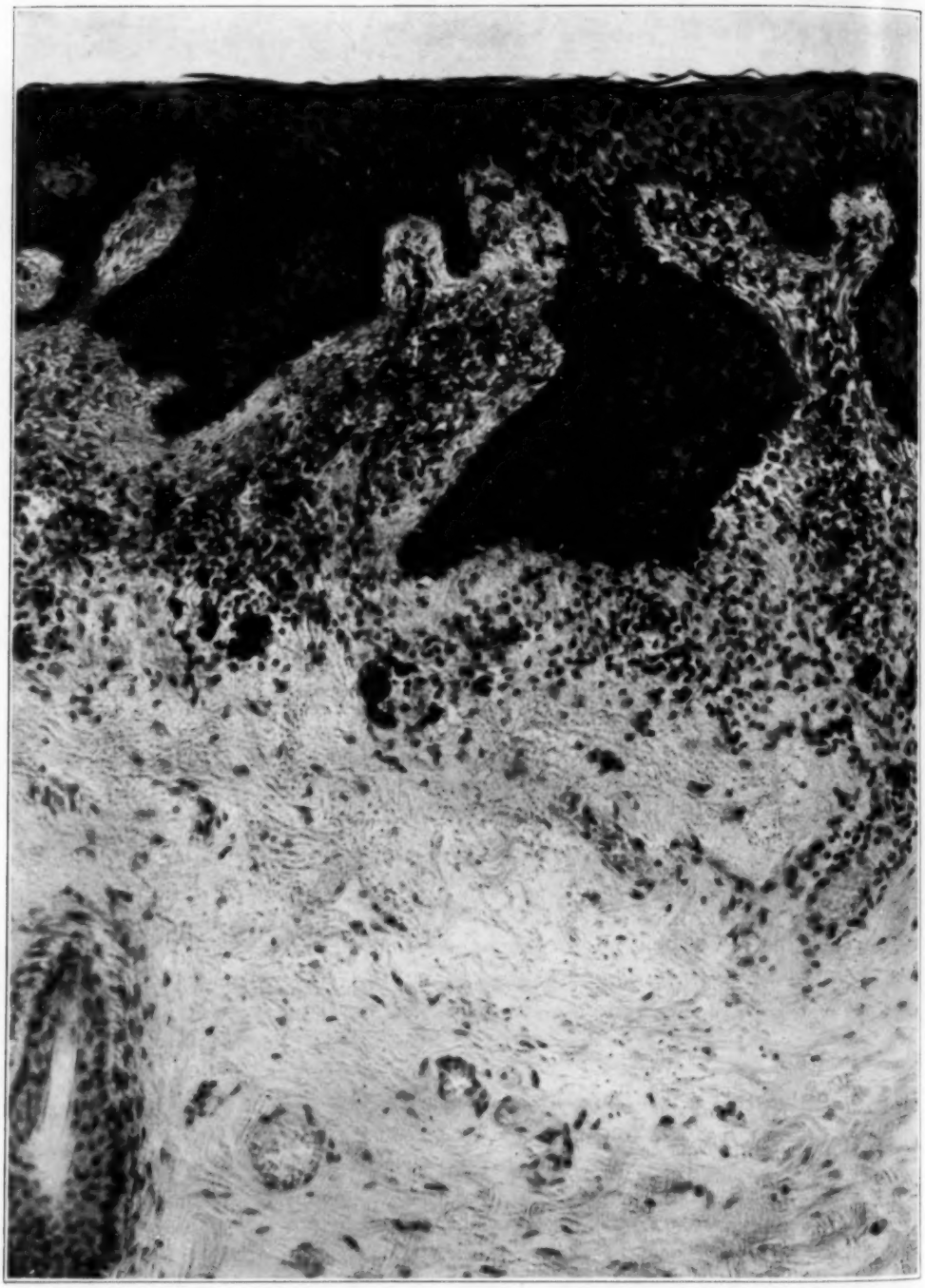

Fig. 2.—Broadening and down-growth of rete pegs with hyperpigmentation of basal layer. Round cell infiltration and pigment-bearing cells are seen in the upper cutis. Early stage of lesion.

in which the rete was many times its normal thickness, numerous pigmented cells were noted in all layers of the rete. In the acanthotic zones mitotic figures confined to the basal layers were more numerous than in adjacent normal areas.

As the center of the lesion was approached, the rete became several times broader than normal, and the pegs distorted and often fused. The fusion was often incomplete, so that cross-sectioned papillae were seen

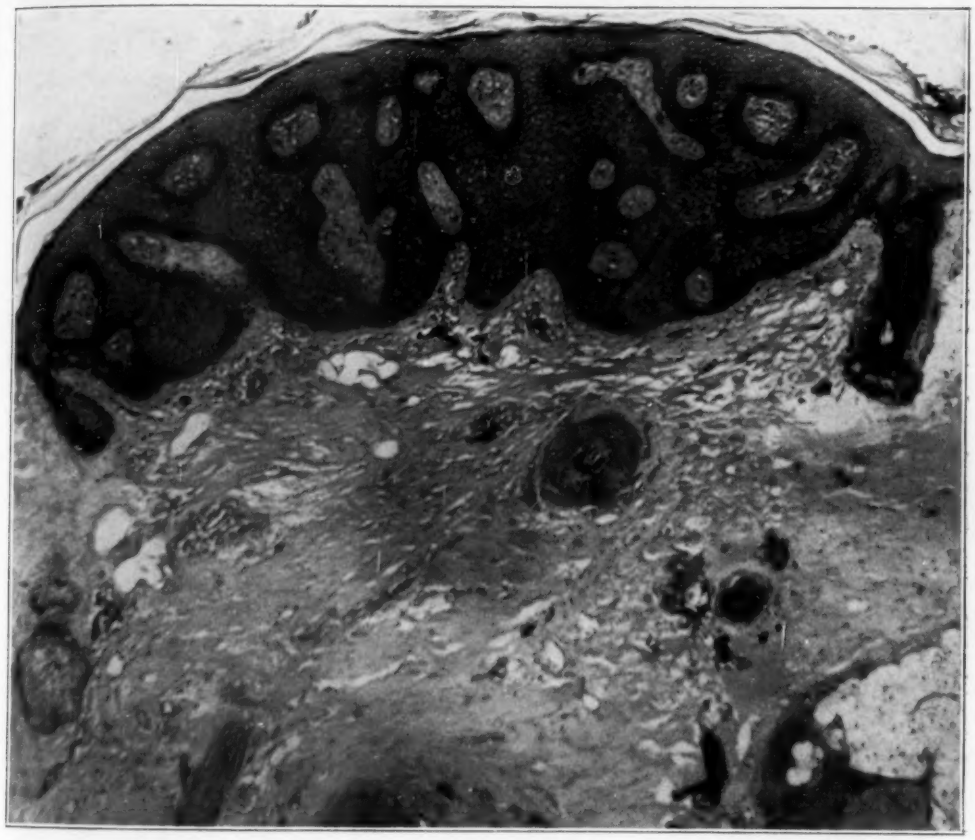

Fig. 3.—General view of entire lesion in moderately advanced stage of development. The irregular acanthosis is limited almost entirely to the rete pegs.

surrounded by epidermal cells (fig. 4). At its full development the epidermal picture resembled that seen in senile keratosis, or in the acanthoid hard nevi (Unna). The irregular acanthosis varied in degree in individual lesions according to our specimens. In one of these it was moderate, while in the other two it was pronounced. There was a mild spongiosis and occasional cells showing perinuclear hydrops. The basal layer was unbroken.

The cutis showed a moderate edema and a number of inflammatory cells in all sections, chiefly in the papillary body. These cells were free in the tissue spaces or surrounded the slightly dilated capillaries. The inflammatory cells were mainly of the small lymphocytic type with a few plasma cells and eosinophils. In many areas, principally just beneath the epidermis, were a number of pigment-containing cells as

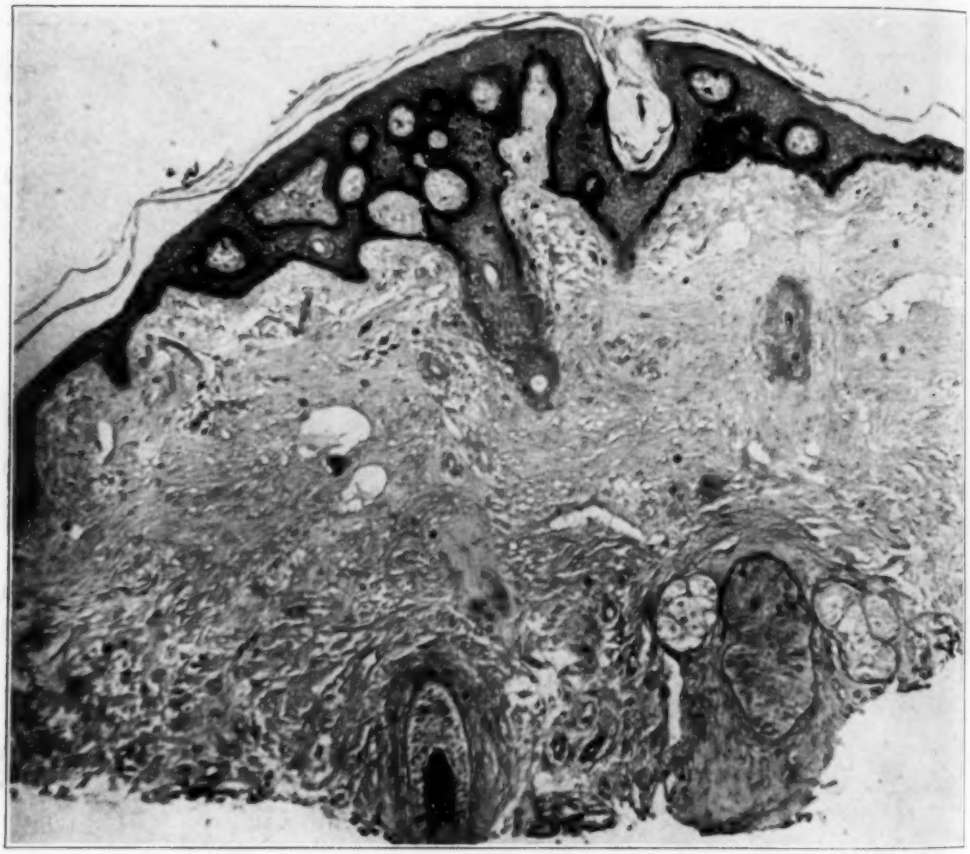

Fig. 4.—Moderately advanced stage. Association of acanthosis with follicles. The lanugo hair follicle shows irregularity of its epithelium and abortive attempt at production of a sebaceous gland.

well as some free pigment granules. This pigment was similar to that in the epidermis. The pigment-bearing cells were large, some spindle or oval shaped. Many were almost completely obscured by the contained pigment. Some of these cells did not look like chromatophores, but resembled the appearance of melanin-forming cells such as are found in mongolian spots; however, most of them were chromatophores.

The collagenous tissue showed changes associated with moderate inflammation, but in addition, there were areas of pronounced homogenization in the upper cutis. In one of the specimens this homogenization resembled the picture seen in colloid degeneration. In one specimen, collastin was present.

The elastic tissue showed moderate fragmentation in the upper cutis, the changes in this tissue being on the borderline of the normal. There

Fig. 5.—Irregular acanthosis with hyperpigmentation and "capping" in the basal layer.

were no nevus cells. In each case the acanthotic areas were in definite relation with the pilosebaceous system, especially the hair follicle (fig. 5). In two of the cases several epithelial strands projected downward from the cutis to connect with the follicular wall in the subpapillary zone. In the third case this feature was absent, but the relation of the epidermal changes to the follicular apparatus was evident. The sebaceous glands showed an increase in the epithelial stroma and islands of miniature sebaceous cells unconnected, apparently, with any follicular system.

In one case, intra-epidermal cysts were a prominent feature. In the markedly acanthotic zone four cysts were noted, two large and two smaller ones. Their contents were cornified material having a lamellar arrangement. One of the larger cysts was directly connected with a hair follicle (fig. 6). In one of the smaller cysts a fragmented lanugo hair was seen. Each of the other two specimens showed a single cyst of the character already noted.

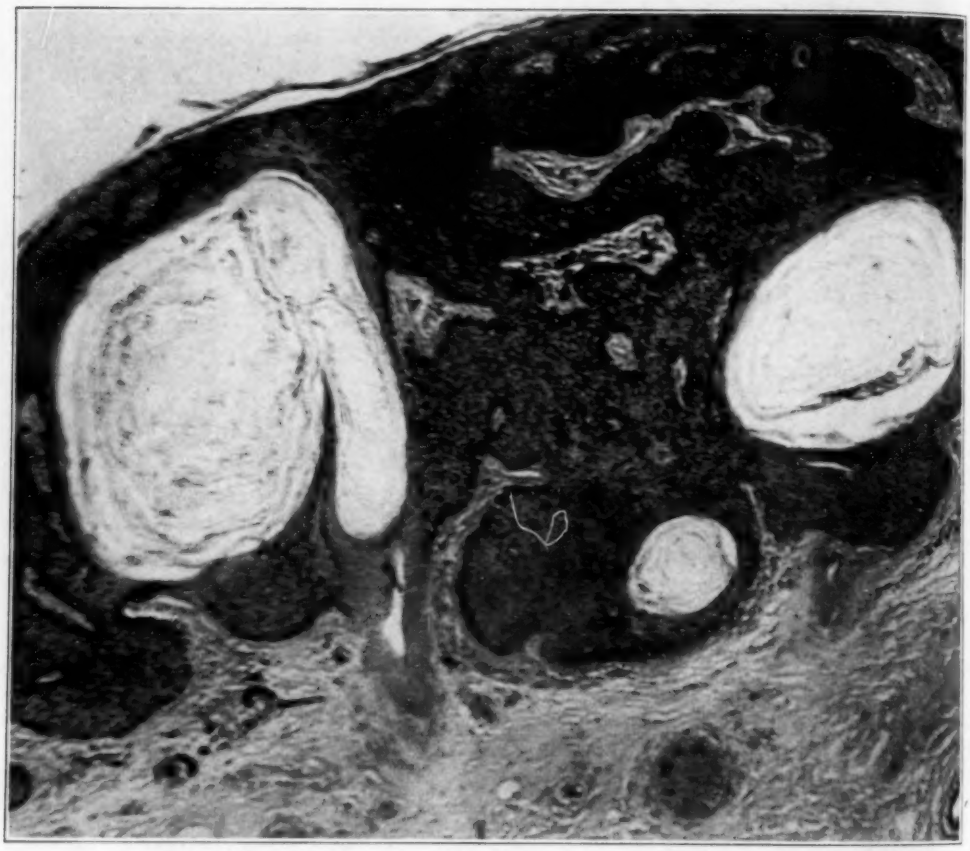

Fig. 6.—Intra-epidermal cysts with concentrically arranged fibrinous contents. One of the cysts is connected with a hair follicle. Pigment-containing cells are seen in rete malpighii.

In two of the cases (both males) rudimentary hair follicles were present, and there was some irregularity and abnormality of growth of the follicular walls. This consisted in lateral budding as if an abortive attempt at the formation of sebaceous glands had occurred. In one specimen, there was slight intercellular edema of the epithelium of the coil glands and sclerosis of the connective tissue septums.

COMMENT ON MICROSCOPIC OBSERVATIONS

In the microscopic study of this disorder we found, as most prominent features, irregular acanthosis, hyperpigmentation, rudimentary hair follicles and immature sebaceous elements. Added to these were a moderate catarrhal inflammation of the cutis and degeneration of the collagenous tissue.

Our conception of the inflammatory feature is that it was the expression of a tissue reaction to epidermal hyperplasia, such as is seen in epithelioma and keratosis senilis. We do not think that it was a response to an infectious agent, which would be the alternative explanation.

The collagenous degeneration may well be the effect of exposure, rather than an integral part of the process. In fact, epidermal atrophy and collagenous degeneration were noted in areas of the section adjacent to but not involved in the lesion. As our material was obtained from the face of adults, this explanation seems most consonant with the results.

The acanthosis, hyperpigmentation of the epidermis and cutis, and the rudimentary pilosebaceous elements suggest to us that the dermatosis is a nevus. In conjunction with the clinical features we will again discuss this question at greater length.

DIFFERENTIAL DIAGNOSIS

The diseases which come into consideration from a differential diagnostic standpoint are not many, and dermatosis papulosa nigra is so characteristic that once it has been seen it should occasion little difficulty diagnostically, with perhaps one exception, adenoma sebaceum.

Moles are round, not angular, and firmer to the touch. Pigmented nevi are macules, not papules. Seborrheic and senile keratosis are scaly or crusted-lesions. The latter, however, show many histologic similarities to dermatosis papulosa nigra. In clinical features alone, verruca plana most nearly resembles this disorder, but the lesions of dermatosis papulosa are always isolated and never linear. The histology of these conditions is dissimilar, since there is no hyperkeratosis in dermatosis papulosa nigra. Multiple benign cystic epithelioma is usually found on or near the eyelids, though it may appear on the cheeks. Its histology, however, definitely distinguishes it. The papular inflammatory diseases which appear on the face, such as acnitis, lupus miliaris disseminatis facei, acne and similar conditions require no serious consideration.

One disease alone must be discussed in some detail. This is adenoma sebaceum. While this disease, so far as location and appearance are concerned (with due regard for pigmentation), occurs in the negro race in its typical form, it also appears in this race, as it does in whites, in aberrant types. We refer to location; namely, the appearance of lesions of adenoma sebaceum on the cheeks, forehead and areas other than the naso-

genial grooves and adjacent surfaces. We have seen an adult negro with lesions exactly like those of dermatosis papulosa nigra, except that they were larger, averaging from 3 to 4 mm. in their longest diameter, in which histologic study showed adenoma sebaceum. At this point, we recall an article by Sutton.[3] In this article, Sutton described and pictured the cases of two negro patients with an eruption similar to dermatosis papulosa nigra. In Sutton's case 1 the lesions looked like "tiny pigmented moles." Histologic study revealed multiple benign cystic epithelioma. In his case 2 the diagnosis of dermatosis papulosa nigra would be justified from the photographic appearance. In this case adenoma sebaceum was found by histologic examination.

From our own case already mentioned and from Sutton's, we think that the deduction can be made that an eruption having the clinical features of dermatosis papulosa nigra may be adenoma sebaceum. There is no absolute differentiation, we think, except by microscopic study.

COMMENT

Having presented our observations on this disorder, we now wish to interpret them. To us, the most interesting questions that arise relate to its nosology and genesis.

What is dermatosis papulosa nigra? In our opinion it is a nevus. This answer, however, deserves some expansion. Its clinical features comport with nevi in that it is a noninflammatory, slowly developing, permanent and circumscribed malformation of the skin. That it is not present at birth or soon after and shows no nevus cells is not, as is well known, against this assumption. Its practical limitation to the negro race is an interesting feature for which we have no explanation. It must be hidden in the darker recesses of genetics. It would be interesting to make certain of the diagnosis by histologic examination in any cases which appear among other than the negro race. The condition in our case in a Mexican and in Castellani's in a European was diagnosed only clinically. There is some question, in view of what was written earlier, whether these were not examples of adenoma sebaceum.

Pathologically, the disorder shows an irregular acanthosis and disturbance of the normal development of the pilosebaceous apparatus with the former overshadowing the latter. Its clinical appearance is produced by changes in the rete malpighii; these changes being in both the body and the pegs of that layer. Dermatosis papulosa nigra, genetically, is an ectodermal nevus, among which we count adenoma sebaceum as an example of the sebaceous glands; nevus pilosus of the hair follicle;

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3. Sutton, R. L.: A Differential Diagnosis of Multiple Benign Cystic Epithelioma and Adenoma Sebaceum in the Negro, J. Cutan. Dis. **29**:480, 1911.

hidradenoma of the sudoriparous glands, and hyperkeratotic verrucous nevus of the epidermis. The latter is a keratoid; dermatosis papulosa nigra, in the main, an acanthoid type of epidermal nevus.

In regard to the time of appearance and development of dermatosis papulosa nigra, some light can be shed by our knowledge of the embryologic development of the pilosebaceous system and the pigmentation of the skin. Our reasoning here is indirect and proceeds from the evident association of the acanthosis and other conditions with the follicular apparatus. We have mentioned this histologic feature in an earlier part of this paper.

It seems permissible to regard the condition as arising from anlage of the pilosebaceous system. Carol [4] assumed this for adenoma sebaceum, suggesting that the rete pegs which he found projecting themselves into the cutis might be regarded as abortive attempts at the production of follicular systems. The same reasoning applies, we think, to dermatosis papulosa nigra. If so, the disturbance must originate between the fifth and seventh months of fetal life. Its clinical development in late childhood and at puberty accords with this line of thought. For then we can seen that it responds to the same impetus that the normal hair and sebaceous elements do at the time of puberty and having reached a certain stage of development it goes no further, but remains unchanged for the remainder of life. We do not think that the occasional cases of its appearance as early as the seventh year conflict with this deduction, since in these cases the disorder has appeared extremely early and has been insignificant; in addition, puberty occurs earlier in the negro than in the white race.

CONCLUSIONS

1. Dermatosis papulosa nigra is a common disorder among negroes, having an incidence of from 6 to 12 per cent.

2. It is more common in females than in males.

3. Histologically, it shows an irregular acanthosis and developmental disturbance of the pilosebaceous apparatus.

4. This dermatosis is a nevus.

We are indebted to Dr. Walter J. Highman, New York City, and to Dr. Hamilton Montgomery, Mayo Clinic, for assistance in the microscopic study, and to Dr. G. C. Lechenger of Houston for the photomicrographs.

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4. Carol, W. L. L.: Beitrag zur Kenntniss des Adenoma sebaceum (Pringle) und sein Verhältnis zur Krankheit von Bourneville und von Recklinghausen, Acta derm.-venereol. **2**:186, 1921.

ABSTRACT OF DISCUSSION

DR. HOWARD FOX, New York: I am interested in this subject because of my long experience in the Harlem Hospital with dermatoses in the negro. I recall having seen these inconspicuous eruptions from time to time. I never performed a biopsy on any of them and have no knowledge of the histologic changes. Recently I asked a colleague at the Harlem Hospital to refer a characteristic case to my clinic. The patient was a full-blooded negress who presented about 200 round, smooth nonitchy lesions which were invariably discrete and showed no evidence of grouping. They were chiefly present on the face and neck. The lesions varied in size from that of a pin point to that of a pin head and were dark brown. The majority were elevated. The patient stated that she did not know of a similar condition in any other member of her family. On examination, her son, aged 6 years, was free of the condition. I had always considered the lesions to be tiny nevi.

DR. FRED WISE, New York: I have had an experience like that of Dr. Fox. During a number of years in the Vanderbilt Clinic, my colleagues and I noticed these lesions but did not pay any attention to them. The Vanderbilt Clinic at that time was situated in a zone with a large negro population.

To show how one might be misled, there was a time when the Sloane Maternity Hospital sent patients to the Vanderbilt Clinic for Wassermann tests, and we noted these facial lesions in women with positive Wassermann reactions. We did not examine them closely, but were inclined to connect the small lesions with pregnancy, but after we had observed them in a few males and nonsyphilitic pregnant women we were set right on that point.

A point Dr. Michael did not mention is the familial occurrence of this disorder. On several occasions we had a brother and a sister with similar lesions, almost identical in appearance. This occurred not only in full-blooded negroes but in mulattos as well. The lesions we saw were polygonal, and I think that it is especially the polygonal and not the rounded lesions to which the essayist refers in his paper.

DR. JEFFREY C. MICHAEL: In regard to the points raised by Dr. Wise, it is the polygonal type of lesions I had in mind. Secondly, so far as the familial characteristic is concerned, the condition undoubtedly is familial, but we were unable to make any definite study of this for it is difficult to trace negro families. That was the great difficulty with the entire study because the disease occurred only in negroes.

A CASE OF DERMATITIS VENENATA DUE TO EPHEDRINE *

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The following case may be of interest as it is the first case of a dermatitis venenata caused by ephedrine observed by me, and it is likely that others have seen or may see similar cases.

REPORT OF CASE

Mr. E. A. N., aged 45, was referred on Feb. 4, 1929, by Dr. John Nelson of New York for an acute dermatitis of the face and hands of two days' duration. The entire face was bright red, swollen and thickly covered with small vesicles from a pinhead to ⅛ inch (0.3 cm.) in diameter. The lower lids were edematous. There was also some edema of the nose and upper lip. There was much burning and itching. The dorsal surfaces of both hands were similarly affected, except that the vesicles were larger. There was a mild seborrhoic dermatitis in the front of the chest of long duration.

Careful inquiry was made as to the usual possible etiologic factors at this time, but no definite cause could be found. The possibility of ephedrine as the cause was not considered. The dermatitis subsided in from three to four days with use of wet dressings of 2 per cent aluminum acetate solution.

On May 21, Dr. Nelson wrote me: "It might be of interest to you to know that my brother had another attack of dermatitis venenata (facial); the cause was ephedrine in oil which he was using for a head cold. He used the ephedrine at night and the skin around the nose and mouth was involved the following morning."

On inquiring from Dr. Nelson whether ephedrine was used before the first attack and what preparation was used, it was learned that his brother did use ephedrine in oil before he developed his first attack of dermatitis venenata. He wrote further: "His last attack, which was mild, followed one spraying of the nose. He stopped when he noticed the irritation but developed typical lesions. I do not know what preparation he used. He says it was in an original package; that he asked for ephedrine in oil for nasal use."

* Submitted for publication, June 15, 1929.

MADUROMYCOSIS

A CONTRIBUTION TO THE STUDY OF MADUROMYCOSIS, WITH REPORT OF A CASE OF INFECTION WITH ASPERGILLUS NIDULANS *

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Since the time of Gill, in 1842, certain parasitic agents belonging to the higher fungi have been described as invaders of the tissues of man and animals. These infections have a tendency to originate in the subcutaneous tissues and to spread by contiguity to adjacent structures. They are characterized by the formation of granulomatous tumors which tend to break down, the resulting discharge containing colored granules or grains made up, at least in part, of fungus elements.

Before the time of Gill these fungus lesions were not definitely differentiated from such other conditions as caused deformity by enlargement such as the various causes of elephantiasis. Something of the nature of the condition was known, however, for such names as "Gootloo Mahdee" (because of the egglike swellings) and "Kirinagras" (dwelling place of worms) had been used by the natives [1] in Ballory and in Rajputana, India, respectively. Then, too, in 1712, Kaempfer, in 1714, the Pondichery missionary, and in 1840, Brett, all had probably noted the disease.[2] But it was Gill of the Madura Dispensary in India who first recognized the gross pathologic changes in a condition of the foot characterized by "marked deformity and fungoid excrescenses discharging an offensive ichorous fluid while internally it caused destruction of the joints, cartilages, and ligaments; the diseased tissue resembling fibrocartilage." [1]

In 1846, the term "Madura foot" was introduced by Colebrook, also of the Madura Dispensary. This term, which is still used, has come to include all fungoid lesions of the feet in which there is grain formation regardless of specific fungus etiology.

In 1860, "mycetoma" or fungus tumor was introduced by Van Dyke Carter as a more appropriate term to describe a disease with black granules. In 1861, he extended this term to include also those infections

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* Submitted for publication, April 4, 1929.

* From the Departments of Clinical Medicine and Dermatology of the University of Wisconsin, State of Wisconsin General Hospital.

1. Chalmers, A. J., and Archibald, R. G.: A Sudanese Maduromycosis, Ann. Trop. Med. **10**:169, 1916.

2. Castellani and Chalmers: Manual of Tropical Medicine, ed. 3, New York, William Wood & Company, 1919, p. 2110-2130.

which discharged yellow or white grains. His classification was based entirely on the color of the characteristic grains in the discharge. Actinomycosis at that time had not been described as a clinical entity, so that the term mycetoma has come to include a group of fungus infections as will be noted later.

Actinomycosis was described as a clinical entity by Bollinger and Harz in 1877 and by Rivolta in 1878 who erroneously were of the opinion that the clublike forms found in certain grains were specifically characteristic of a definite parasite, *Actinomyces bovis* of Harz and *Discomyces* of Rivolta.

Boyce and Surveyor, in 1894, "first proved that the fungi existing in black and yellow grains were quite different and thus definitely established the two main divisions of mycetoma which today we call maduromycosis and actinomycosis." [1]

In 1913, Pinoy [3] divided mycetoma into two groups: actinomycosis and true mycetoma.

Under the actinomycoses he included those infections characterized by grains formed of fine, nonseptate filaments arranged definitely into a central and a peripheral portion, the central portion being made up of a network of fine, ramified gram-positive threads, which can be divided into long or short segments to give the appearance of bacilli or cocci. The terminations of these filaments in the peripheral portion are swollen to form a wreath of small clublike forms. In differentiating actinomycosis from true mycetoma, Pinoy limited the term actinomycosis to those grains caused by fungi which he feels belong to the same lineage, which are of common stock with bacteria and which cannot be classified with the molds. His observations were made from nineteen cases in cattle, in thirteen of which he found *Cohnistreptothrix israeli,* two *Nocardia,* one mixed, and three *Actinobacillus lignieresi;* and from three cases in man in two of which he found *Cohnistreptothrix israeli.* From these observations he stated that *Cohnistreptothrix israeli* is the most frequent but not the only cause of actinomycosis.

True mycetoma, on the other hand, Pinoy described as that malady the grains of which are formed by larger and by segmented filaments with a definite membrane, which filaments when examined after treatment with potassium hydroxide appear to be of segmented mycelium carrying some large swellings.

To avoid confusion between the term true mycetoma introduced by Pinoy and mycetoma of Van Dyke Carter, Chalmers and Archibald,[1] in 1916, introduced the term "madrumycosis" [4] for true mycetoma; and

3. Pinoy, E.: Actinomycosis et mycetoma, Bull. de l'inst. Pasteur **11**:929 and 977, 1923. Brumpt, E.: Precis de parasitologie, ed. 3, Paris, Masson & Cie, 1922.

4. Maduromycosis is sometimes spelled maduramycosis.

continuing with the classification of Pinoy, defined mycetoma as including "all growths and granulations producing enlargement, deformity and destruction in any part of the body of man, brought about by the invasion of the affected area by certain species of fungi belonging to different genera, which give rise to variously colored and shaped bodies called grains, which are formed of hyphae with or without chlamydospores and are found either imbedded in the pathological tissue forming the growths and granulations or escaping freely in the discharge from the diseased area." [1]

It seems that the present conception of maduromycosis (true mycetoma) is derived chiefly from studies made on the clinical condition, Madura foot, for when molds invade other parts of the body than the foot, enlargement and deformity have not necessarily been present. Therefore, the presence of maduromycosis in such places has not always been recognized. Then, too, as will be noted later, the grains are not always made up of hyphae.

For the present consideration the broad definition of Chalmers and Archibald might be enlarged to include all growths and granulations which may produce enlargement and deformity in any part of the body of man, brought about by the invasion of the affected area by certain species of fungi belonging to different genera, which give rise to variously colored and shaped bodies called grains, which are formed in part of fungus elements usually of hyphae with or without chlamydospores, and are found either embedded in the pathologic tissue forming the growths and granulations or escaping freely in the discharge from the diseased area.

True mycetoma and maduromycosis, it is evident from the foregoing, are terms which do not indicate specifically a definite etiology for a clinical entity. The chief characterizing factor in the recognition of this disease, usually manifested as Madura foot, is still the typical grain formation as at the time of Van Dyke Carter, except that actinomycosis, as noted previously, has been separated as another entity.

Maduromycosis has been divided into three types: the black grain maduromycosis, the yellow or white grain maduromycosis, and the rare red grain maduromycosis. This classification is of value chiefly for clinical study and classification, although attempts have been made to group various fungi with the occurrence of the variously colored grains. The variations in the color of the grains as yet are of little help in the identification of the etiologic fungus, and as Pinoy has stated, "a distinction of mycetoma by the color of grains is superficial," for not only do different fungi produce grains of the same color, but "the same fungus may produce grains of different color."

Using cultures of *Aspergillus (Sterigmatocystis) nidulans* from a case of mycetoma with white grains studied by Nicollei and Pinoy, Pinoy

was able to produce, in the foot of a pigeon, lesions with both black and white grains. To help substantiate his contention, I have a case with black grains, the cultures from which Charles Thom has identified as *Aspergillus (Sterigmatocystis) nidulans.*

Even though the color of a grain or its gross characteristics do not aid in the recognition of the specific underlying fungus or fungi, it is from the grain alone that satisfactory material is obtained for mycologic study; for it seems that just as pus is the expression of localized bacterial infection, so the grain is the expression of a fungus lesion.

The literature in regard to the classification of these fungi is still in a state of confusion, for frequently the same fungus appears under different names, and in many reported cases data have been insufficient to identify the etiologic agent. Gammel [5] quoted the following nine different genera as having been described as causative agents: *Madurella, Indiella, Glenospora, Scedosporium, Allescheria, Pennicillium, Aspergillus* and *Sterigmatocystis.*

For the present consideration *Sterigmatocystis* will not be grouped as a separate genus, but, after Thom and Church,[6] as a species of *Aspergillus.* They noted that Cramer,[7] who first described *Sterigmatocystis,* in 1859-1860, separated *Sterigmatocystis* from *Aspergilli* as a different genus because of the development of secondary sterigmas on the head of *Aspergillus.* They felt with Wehmer [8] that "this basis for separation would put into different genera species which are obviously closely related," for "there are sections of *Aspergilli* with consistently one series of sterigmata and other sections with sterigmata in two series, but there are also *Aspergilli* in which heads of both kinds are found in the same culture and sterigmata of both kinds in the same head." [6] They expressed the feeling that there is no advantage in maintaining the separate genus. Henceforth *Sterigmatocystis nidulans* in this paper will be considered to be a species of the genus *Aspergillus* as *Aspergillus nidulans* in accordance with their classification.

This mold, of which at least eleven varieties are now known, was first described in 1859-1860 as *Sterigmatocystis,* but it was more exten-

5. Gammel, J. A.; Miskdjian, H., and Thatcher, H. S.: Madura Foot (Mycetoma): The Black Grain Variety in a Native American, Arch. Dermat. & Syph. **13**:66 (Jan.) 1926.

6. Thom and Church: The Aspergilli, Baltimore, Williams & Wilkins Company, 1926, pp. 4-6, 7, 12, 20, 21, 28, 49, 55, 62, 68, 84, 132, 138.

7. Cramer, C.: Vierteljahresschrift der Naturforsch. Ges., Zurich, 1859 and 1860.

8. Wehmer, C.: Die Pilzgattung Aspergillus in Morphologischer, physiologischer und systematischer Beziehung (in Mémoires de la société de physique et d'histoire naturelle de Genève, vol. 23, part 2, no. 4), Geneva, C. Eggimann & Cie, 1901.

sively studied by Eidam,[9] in 1883, as *Sterigmatocystis nidulans.* He first studied the mold saprophytically and later determined its pathogenicity by injecting cultures intravenously into two rabbits, from which he recovered both spores and mycelium to prove that the mold would develop in animals with the growth of both mycelium and conidian forms. From this experimental evidence, he compared its pathogenicity with that of *Aspergillus fumigatus.*

The only record of the occurrence of this mold clinically in man as mycetoma was made by Nicollei and Pinoy, in 1906, when it was identified with white grains in a lesion on the foot of a Tunisian woman. The implantation of the mold in this case was believed to have been effected by the impregnation of a fragment of barley plant in the sole of the woman's foot while she worked barefooted in the barley fields. In nature, however, its occurrence has been noted frequently, so that it may be considered to have the same distribution as other *Aspergilli,* occurring in the culture tubes as a laboratory "weed," in foodstuffs, in the soil, and even in bees' nests from one of which in the Breslau Botanical Gardens, Eidam obtained material for his studies of *"Sterigmatocystis."*

The incidence of mycetoma chiefly as Madura foot has been extensively studied. Castellani and Chalmers, referring to the black grain maduromycosis, noted its incidence in Europe, Asia, Africa and America. Although not limited to any continent or climate, it has been found chiefly in the dry parts of the "Zone of Northern Hot Summers," where the natives are accustomed to go barefooted. Its frequent observation in the Northern hemisphere in such widely separated places as Southern India, Northern Africa, Khartoum, the southern part of North America and Europe indicates that it is widely distributed rather than that it is limited to regions in which there are observers to describe it. Factors of significance in the incidence of the disease seem to be its occurrence chiefly on the sole of the foot, frequently in laborers, and frequently following an injury when a foreign body, such as a thorn, a piece of grain stalk or some dirt might be introduced into the wound. The presence of a foreign body as a factor is borne out otherwise by the experiments of Pinoy, who was unable to reproduce the disease with *Aspergillus (Sterigmatocystis) nidulans* until he introduced a piece of reed at the site of inoculation.

In North America the disease has been encountered forty-two times. In all but four of these cases it developed in the South, while one occurred as far north as Canada in a patient who had never been out of the Dominion. In all except one, in which the hand was involved,

9. Eidam, E.: Zur Kenntniss der Entwicklung bei den Ascomyceten, Beiträge Biologie der Pflanzen, Cohn, 1883, vol. 3, p. 377 (figs. XXI and XXII).

the disease was in the foot and usually on the sole. The great majority of the cases were in Mexicans.

Boyd and Crutchfield [10] have studied mycetoma particularly as it has occurred in North America, where they collected thirty cases. Since then twelve more have been recorded, so that, with the case to be reported here, forty-three in all have been noted.

Gammel has concluded that eighteen of twenty-one cases of mycetoma that occurred in the United States were actinomycoses, while only three were maduromycoses. To these three cases five more must be added to three of which he drew attention, one of which has since been reported by Thompson and Ikeda; one under the observation of Crutchfield and the third to be reported here. Two more cases both of the black grain variety of mycetoma occurring in the foot have been reported since then in 1927 by C. R. Halloran of California and by C. C. Harrold of Georgia. These cases are classified as maduromycoses only because of the color of the grains.

Six of the eight cases of maduromycosis that occurred in the United States were of the black grain variety; the other two were of the white grain variety, namely, that of Boyd and Crutchfield due to *Allescheria boydii* and that of Crutchfield, not published, reported by Gammel as being due to an unidentified organism. The six cases of maduromycosis caused by fungi producing black grains are those of Wright, Gammel, Thompson, Ikeda, Halloran, Harrold and my case. Wright's [11] case reported in 1898 from Boston in an Italian woman has been considered by Boyd and Crutchfield to have been caused by *Madurella.* The organism, however, was not completely identified. Gammel's case reported from Cleveland in 1926, likewise, was caused by an infection by a new species—*Madurella americana.* In 1927, Gammel [12] reported his identification of the organism from the third case as due to another new species of *Madurella* to which he gave the name of *Madurella ikedai.* This case was later reported by Thompson and Ikeda [13] from Minneapolis. Halloran cultured a fungus from his case as a streptothrix,

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10. Boyd, Mark F., and Crutchfield, E. D.: A Contribution to the Study of Mycetoma in North America, Am. J. Trop. Med. **1**:215, 1921. Lovejoy, E. D., and Hammack, R. W.: Mycetoma: Report of Four Cases, Arch. Dermat. & Syph. **11**:71 (Jan.) 1925. Pagenstecher, G. O.: Madura Foot More Properly Called Mycetoma, J. A. M. A. **78**:1363 (May 6) 1922; Third Case of Mycetoma, ibid. **82**:1692 (May 24) 1925.

11. Wright, J. H.: A Case of Mycetoma (Madura Foot), Tr. A. Am. Phys. **13**:471, 1898.

12. Gammel, J.: The Etiology of Maduromycosis; with a Mycologic Report on Two New Species Observed in the United States, Arch. Dermat. & Syph. **15**: 241 (March) 1927.

13. Thompson, H. L., and Ikeda, K.: Maduromycosis: Fourth Case Reported in the United States, Arch. Surg. **16**:764 (March) 1928.

while Harrold was unable to obtain growths on culture. In the present instance, the fourth case of maduromycosis with black grains to be reported in North America, *A. nidulans* was found. This is the second time that *A. nidulans* has been known to cause a maduromycosis, and the first time that it has occurred clinically with black grains.

REPORT OF CASE

Miss R. F., a university student, aged 19, white, a native-born resident of New York, had never been south of New York until after the onset of the present condition. From February, 1923, prior to which time she was well, until July, 1924, a series of six lesions developed on her nose, cheeks, behind the right ear, and on the extensor surface of the right forearm. These lesions first manifested themselves as "boils," "deep abscesses" or as "hard lumps," which on drainage instead of healing, burrowed farther under the skin to form "channels." They all ran a course of several months, some healing spontaneously and others healing after extensive incision and packing with iodoform gauze. Other local antiseptics, such as iodine, mercurochrome-220 soluble and silver nitrate, had no effect. One lesion, that on the right forearm, healed only after the "channel" formed had been incised in five different places. Barring two small transient lesions, the patient stated that she was free from infection during the summer of 1924 until November, when, following a blow by a hockey stick back of the right ear, the trouble reappeared at that site. (This was the only injury associated with the disease.)

The patient came under my observation on Nov. 17, 1924, at which time she had two furuncle-like lesions which had been widely opened four days previously. Both lesions were filled with a thick, dirty (blackish) pus and resembled infected cysts rather than furuncles.

By January, 1925, these lesions had healed spontaneously, but three more soon developed about the right ear. One of these was above the ear, another in front of the ear extending from the tragus to the level of the lower margin of the auricular lobe, and the third was behind the ear extending from below the tip of the mastoid over the mastoid almost to the superior attachment of the pinna. The latter two persisted until June, 1925, when they gradually healed, and the disease again became quiescent during the summer.

From these lesions a copious thick, dirty, purulent discharge exuded, drying on the surface to form a dark crust which sealed the sinuses. This sealing of the surface of the lesions together with the formation of an abundance of pus seemed to cause their extension subcutaneously.

With the recurrence of lesions in January, 1925, it was observed that the fine granular particles, which gave the dirty appearance to the pus, at times became massed to form small, soft, caviar-like bodies (grains). The persistence of these bodies and the unusual color of the pus indicated to me that more than an ordinary pyogenic organism was a factor in the chronicity of the infection. When Dr. Otto H. Foerster saw these black grains in April, 1925, he immediately suggested the existence of a black grain fungus, a mycetoma similar to the foot disease—Madura foot.

From October to December, 1925, a series of recurrent lesions developed about the sites of the old scars on the extensor surface of the right forearm (fig. 1). These were typically like those of previous occurrences.

On Dec. 12, 1925, the infected tissue was widely excised by Dr. Jerome Head.

Three lesions about the right ear recurred during November, 1925, and were similar to those of the winter of 1924-1925. Despite what appeared to be thorough excision of the infected areas in February, 1926, the infection persisted until June, 1926, when all lesions quickly subsided. In September, 1926, the disease recurred again behind the right ear. With the sinus formation this time there was also slight swelling. In May, 1927, this lesion was again excised; the wound was left

Fig. 1.—Appearance of right forearm, Oct. 20, 1925, showing active lesions and scars from lesions previously healed. Scars are marked with ink.

open and was packed with iodoform. In September, 1927, after a period of several weeks when it appeared that a cure had been effected, the characteristic dirty-appearing, grain-bearing pus reappeared.

Final excision was performed in April, 1928, when Dr. E. R. Schmidt, who had performed each previous operation about the ear, made a more extensive excision to include a considerable margin of healthy-appearing tissue about the ramified communicating sinuses. All of the tissue above the mastoid to beyond the hair line and including the upper fibers of the sternocleidomastoid muscle, the posterior

part of the parotid gland, and an enlarged lymph gland below the tip of the mastoid was removed to leave a large beveled saucer-like open wound. This was kept constantly filled with iodoform over which was packed iodoform gauze. Healing by granulation without infection or recurrence for a period of over eleven months during seasons of the year when for five years previously the disease had been recurrent seems to indicate that a cure has been effected.

A right otitis media of pyogenic origin which has persisted to date with one short remission developed in 1926. No grains were ever recovered from the ear

Fig. 2.—Same as figure 1, Jan. 22, 1926. Forearm healed with scar formation and free from infection following excision of lesions, Dec. 12, 1926. Lesions about elbow are abrasions from injury.

canal, nor was the discharge at any time from the ear canal similar to that from the sinuses.

The onset of the disease six years before was insidious. Although there was no definite history of an inciting injury, its return in October, 1924, followed a blow with a hockey stick over the right mastoid region. Only since then have my co-workers and I known definitely of the existence of black grain, and of the unusual dirty-appearing pus.

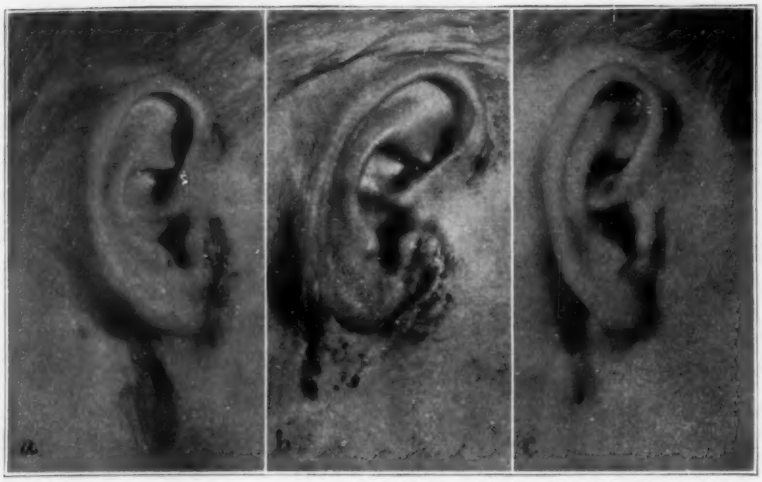

Fig. 3.—(*a*) Appearance of recurrent lesions, Jan. 22, 1926, about right ear before crusts were removed for dressing. An old scar can be seen over right zygoma from a healed lesion. Other markings are from acne. (*b*) Same as in (*a*) a week later after removal of crusts and grains for dressing. Detail is obscured because of the constant oozing of a thin, oily sanious discharge. The walls of the sinuses are friable and vascular so that complete removal of the dried exudate would cause hemorrhage. The dark color is due mostly to blood. (*c*) Appearance of lesions on April 12, 1926. The lesion in front of the ear has become quiescent temporarily. The lesion behind the ear has extended subcutaneously to form a new crater below the lobe of the ear. Here can be seen a typical grain in situ with slight swelling about it. To expose the grain only the overlying skin was incised. A definite sinus unites the two openings subcutaneously.

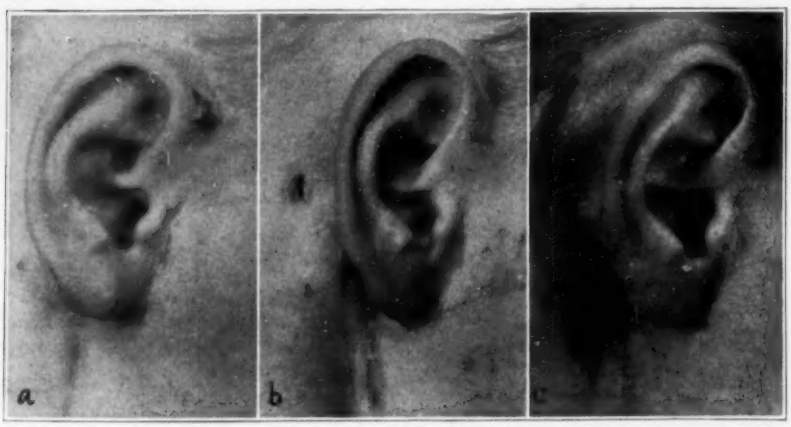

Fig. 4.—(*a*) Grain in situ in lesion above ear. Lesion behind ear is obscured by pinna. (*b*) Appearance, June 16, 1926. All lesions apparently healed during summer, the dark scabs being about ready to drop off. (*c*) Appearance on final discharge, July, 1928.

The infection has manifested itself chiefly in the subcutaneous tissues and has burrowed with sinus formation just beneath the skin to form new sinus openings through the skin along the line of infection. The occurrence of lesions on the forearm as well as on the face suggests the possibility of a hematogenous infection. Such mode of spread would be unusual, for this disease manifests itself characteristically as a localized infection. The forearm more probably was infected secondarily from the face by being scratched by contaminated finger-nails.

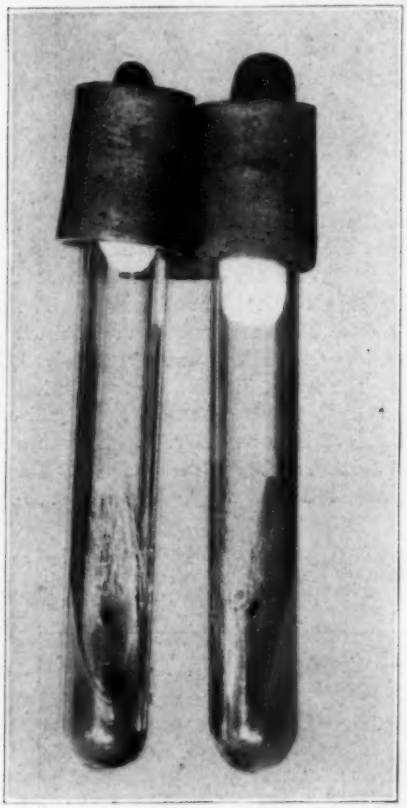

Figure 5

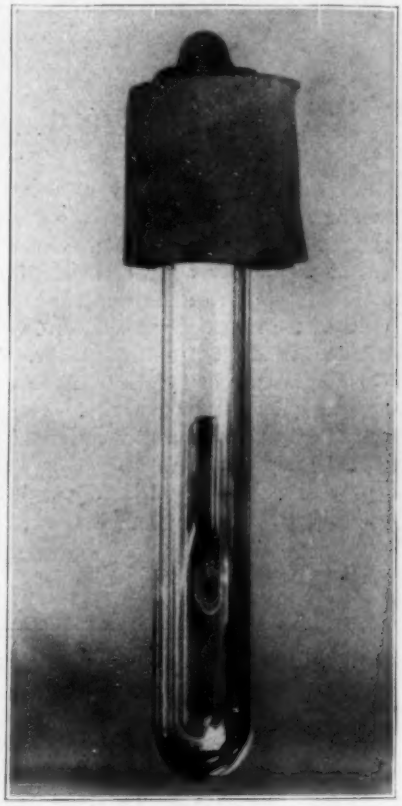

Figure 6

Fig. 5.—Appearance of grains on removal from sinus.

Fig. 6.—Grain cultured for seven days on beef extract agar. Outer growth is of *Staphylococcus aureus*. The darker, smaller overgrowth is of *Aspergillus nidulans* growing from grain beneath. This growth started after five days' incubation.

In their earliest manifestations the lesions resembled furuncles or subcutaneous abscesses, but no tumor nodules appeared. Pain and tenderness were the first symptoms, usually followed within twenty-

four hours by redness and slight swelling. If the infected area was not drained, the infection spread rapidly, breaking down the subcutaneous tissue more extensively until it burrowed through the skin. Even when a lesion was drained, there was a tendency for the discharge to dry and to seal the surface so as to prevent drainage and to cause the sinus to extend farther. In a similar manner the extension of infection was enhanced by the tendency of the margins of the skin about the orifice of a sinus to heal and to close the orifice. At one time, there were five sinus openings on the right forearm, which were all united subcutaneously. Although the extension of a sinus seemed to follow the

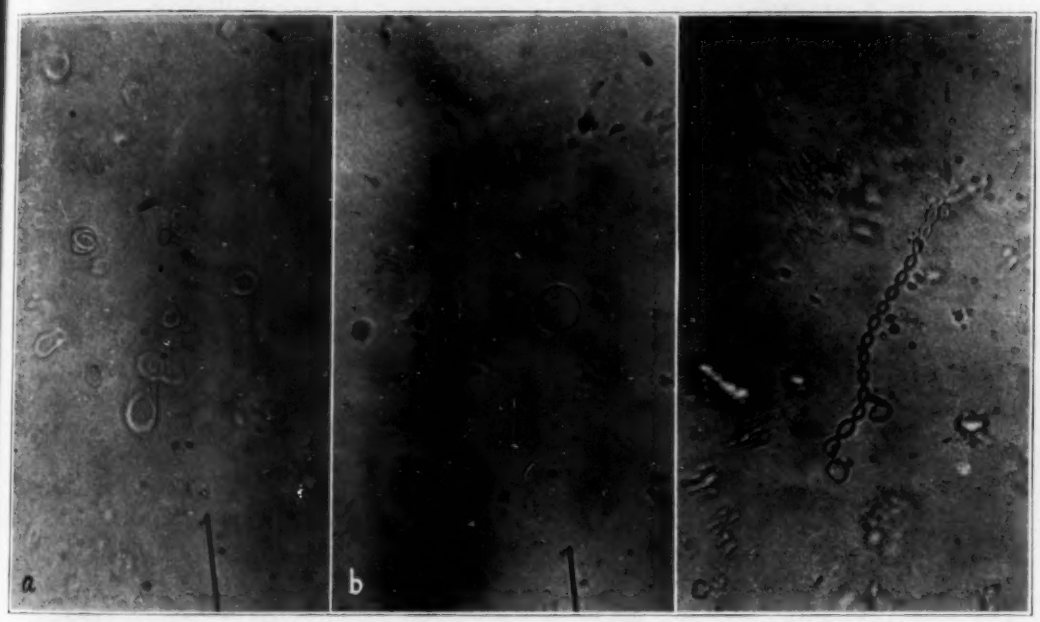

Fig. 7.—(*a*) Yeastlike, spore bodies from grain treated with 40 per cent potassium hydroxide for from two to seven days. Photomicrograph (10 × 95) shows unstained preparation suspended in 40 per cent potassium hydroxide. (*b*) Same as (*a*), showing spore with two exospores. (*c*) Same as (*a*) and (*b*), showing a chain of spores.

closing of its orifice, it also extended but more slowly when it could be kept clean, for frequently at the base of a main sinus crater small secondary sinuses could be probed as far as 3 and 4 cm., never extending, however, deeper than the subcutaneous tissue. The walls of the sinuses have been friable with a tendency to bleed easily, so that the discharge at times has been sanious and the dried crust covering the orifices black, both from dried blood and from fungus material. Sometimes it had been difficult to observe grains because of dried blood about

a lesion. When a sinus is freshly cleaned, the discharge is thin, oily and sanious. Soon, however, it becomes thickly purulent, and after twelve hours will contain the black, coal-dustlike fungoid material, or even grains. The grains, however, can be observed best twenty-four hours

Fig. 8.—Cross-section through black grain. Note the polymorphonuclear cells about the periphery and heterogenous mass of necrotic tissue and débris of the grain proper. The white areas are artefacts. Photomicrograph (10 × 10), shows about two fifths of the entire cross-section.

after a dressing. They appear deeply embedded but visible in sinus niches, escaping freely in the discharge, and commonly in nests of three or four just beneath the concavity formed by the arching of a crust over a sinus orifice.

Irrespective of treatment the infection has recurred each autumn, been worse during the winter and improved or subsided entirely during the summer. On healing, the only evidence of a previous infection has been a narrow linear scar, such as might result from the healing of an incised furuncle.

Fig. 9.—Photomicrograph (10 × 45), showing more in detail a small typical section of the grain shown in figure 8, lacking architectural arrangement and composed largely of necrotic tissue.

CULTURAL STUDIES

I am not qualified as a mycologist to discuss in detail the morphologic and cultural characteristics of *Aspergilli*. Dr. Charles Thom, however, has identified *Aspergillus* grown from three different grains as of the species *A. nidulans*. My co-workers and I had obtained these growths

in pure culture by suppressing bacterial growth on acid mediums. Dr. Thom's characterization of the species follows:

> Colonies on Czapek's solution agar, white to yellowish green, or fairly deep green, velvety to more or less floccose in purely conidial areas, becoming definitely floccose when perithecia are forming or in strains predominantly ascosporic, floccose, with conidium production much reduced and green color absent or nearly so; reverse and agar usually more or less reddish to dark red or reddish brown; conidiophores more or less flexuous with the walls colored in shades of cinnamon brown, septate or unseptate, commonly 50 to 100, less often 200μ long by about 3 to 5μ in diameter, increasing gradually to a domelike vesicle 7 to 15μ in diameter, bearing sterigmata in two series, parallel with axis of the stalk; primary sterigmata varying 5 to 8μ by 2 to 3μ; secondary sterigmata, 7 to 10μ by 2 to 2.5μ; conidia globose up to 3μ or 3.5μ, occasionally to 4μ in diameter, smooth or rough, greenish, in parallel chains adherent into a solid column 30 to 50μ in diameter and up to 100 to 200μ in length.

He stated further:

> . . . The perithecia were not found, hence the description of the perithecia of this series is not given here, but examination of your culture showed the immature phases of ascospore formation. . . .

Unless the existence of a fungus in lesions of this type is suspected, fungus growths rarely will be obtained by ordinary methods of bacterial study. Such pus-producing organisms as the staphylococci on such mediums as beef extract agar with a hydrogen ion concentration of p_H 7.4 to 7.6 grow earlier and more luxuriantly, and, therefore, will obscure or prevent the growth of a fungus. To prevent this early overgrowth by schizomycetes, the mediums used should have a hydrogen ion concentration of p_H 3 to 4 whereby fungi will grow to the exclusion of pus producers. Occasionally, however, both will grow as if symbiotically, as in figure 10, which shows a seven day growth of *Staphylococcus aureus* with a two day growth of *A. nidulans,* superimposed in the center from an underlying grain.

Although cultures were obtained on ordinary mediums, such as beef extract agar, used for the growth of bacteria, most luxuriant growths of *A. nidulans* isolated were obtained on malt extract agar, and most colorful growths on potato and on potato agar. The malt extract agar used consists of: distilled water, 1000; Trommer's malt extract, 25; Bacto agar, 15 and lactic acid to bring the acidity to p_H 3 to 4.

ANIMAL EXPERIMENTATION

Attempts to reproduce the disease in guinea-pigs with the formation of lesions similar to those in the human being have been unsuccessful. Tests as follows were made: (1) intradermal injection with *Staphylococcus aureus* cultured from purulent discharge; (2) intradermal injection with cultured *A. nidulans;* (3) intradermal injection with *Staphylo-*

coccus aureus and *A. nidulans;* (4) implantation of *Staphylococcus aureus* on cutaneous scarifications; (5) implantation of *A. nidulans* on cutaneous scarifications; (6) implantation of *Staphylococcus aureus* and *A. nidulans* on cutaneous scarifications; (7) intraperitoneal injection of *A. nidulans;* (8) injection of *A. nidulans* in sole of hind foot; (9) intradermal injection of dried macerated exudative crusts from

Fig. 10.—Overgrowth of epithelium about edge of sinus behind ear. Photomicrograph (10 × 10) from section of tissue removed, April 6, 1926.

patient; (10) injection of macerated exudative crust in sole of hind foot and (11) injection of macerated exudative crust from patient fortified with cultured *A. nidulans* into sole of hind foot.

None of the pigs developed a lesion as a result of the tests made. One died in less than twenty-four hours from pneumonia. The others lived for five months, when two died of an acute infection. No intravenous injections were made.

Dr. W. D. Stovall likewise injected guinea-pigs with bacterial cultures obtained from the sinuses, and also with infected tissue removed from the right forearm. His guinea-pigs also were resistant.

MORBID ANATOMY

Examinations were made from infected tissue excised from behind the right ear in 1926 and in 1927. Grossly, there was not the deformity from swelling and enlargement usually present in foot lesions of this type. No doubt this was partly due to good dependent drainage which is not present in the foot. The forearm, however, without as good drainage was just as free from swelling and deformity as was the face. Contrary, likewise, to most reports of this disease on section, the tissue was never nodular; the chronic inflammatory reaction was that of an infectious granuloma with the formation of many giant cells, and with an infiltration of small round cells, leukocytes, and mononuclear phagocytes chiefly in the subcutaneous tissues, areas of which were necrotic. In one giant cell observed there were two sporelike foreign bodies. Many more of these sporelike bodies of fungus material were observed concentrated in the interspaces between tissue cells where there was greatest leukocytic infiltration and necrosis in the tissue lining the sinuses. They quickly disappeared or were observed only occasionally when inflammation was less marked. The leukocytes, many of which were fragmented, were chiefly neutrophilic, but in some regions there were many eosinophils. Although clinically there seemed to be little tendency for repair or overgrowth, histologically, there was a peripheral increase in connective tissue with many fibroblasts and lymphocytes about the central areas of necrosis and inflammation. The deeper muscular tissue was uninvolved, whereas the skin at its margin alone showed an overgrowth of epithelium beyond which in the most superficial subcutaneous tissue the inflammatory reaction extended beneath the normal appearing papillary layer.

GRAINS

The process of granule formation in this case seems to be the same as that of grain formation in other similar infections. To apply, however, the term "grains" to these granules the definition of Chalmers and Archibald, as indicated previously, will still further have to be broadened so that grains may consist not only of hyphae and chlamydospores but of other fungoid elements with or without hyphae and chlamydospores. The fungoid material, which could almost constantly be determined, appeared conglomerate as ovoid grains averaging 1 mm. or less in diameter or as almost invisble specks like coal dust or gun powder. Sometimes two or three grains appeared massed to form a black body of 2 mm. or more. This material was soft and cheesy in consistency, but when spread thinly between two slides had a gritty feeling.

When fixed and sectioned, it appeared as massed debris and necrotic tissue fibers surrounded by a layer of polymorphonuclear cells, but when treated with 40 per cent potassium hydroxide for from two to seven days, many spores and sporelike bodies were found as shown in

Fig. 11.—Section of granulomatous tissue removed in 1926, showing in the center of the plate a deeply stained spore shaded on one side (10 × 45).

figures 11, 12 and 13. Although (as Pinoy has pointed out) the size of spores may be varied by their fixation or treatment with solutions for study, these spores do not appear to be conidia; they are too large. Likewise the presence of a chain of spores as seen in figure 13 would

suggest a chain of conidia were they not so large; they appear more like *Monilia*. The spores shown in figure 11 are not unlike those seen in other fungus diseases given such names as blastomycosis.

It should be noted also that when the crusts, which covered the lesions and which were made up in part of grains, were similarly treated, the same sporelike forms were found. The presence of these

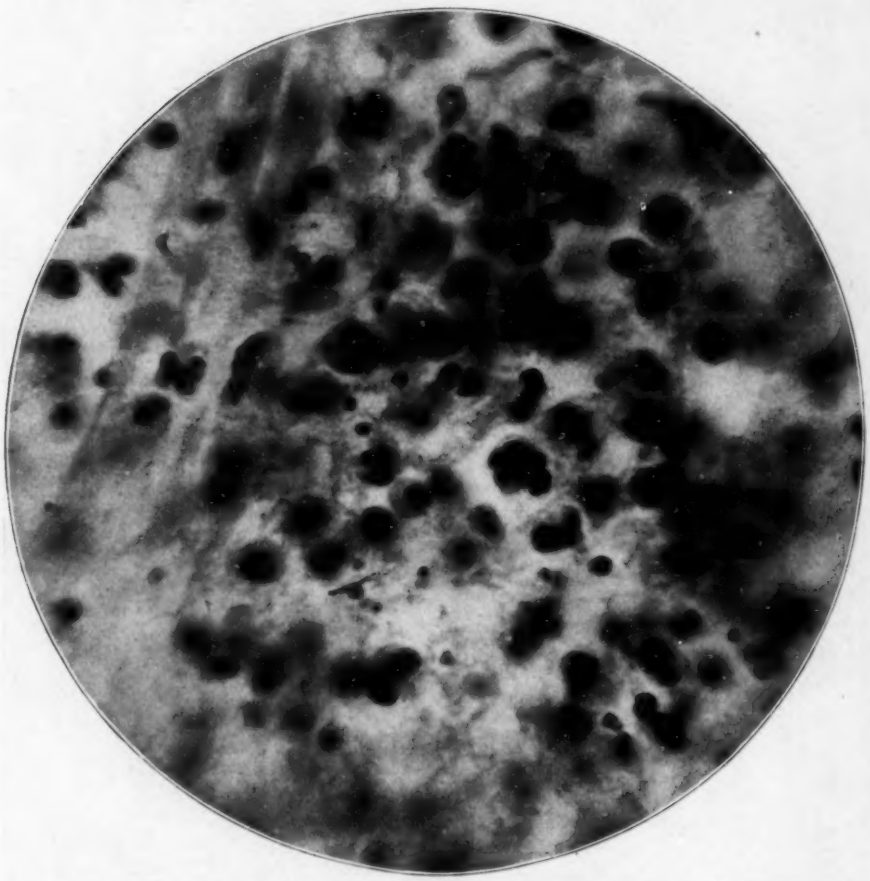

Fig. 12.—Section of granulomatous tissue removed in 1927, showing several spores distributed throughout the field. Magnification about × 1,000.

spores in the exudate from the sinuses was the first proof that one of the higher fungi was the cause of the disease.

No hyphae were observed either in the grains or in the tissue excised, but the many spores found in the regions of most marked inflammation were considered to be of fungus origin. These spores were spherical in shape and comparable in size with the conidia

observed in cultures. In addition to being free from cytoplasm they were too small to be cell nuclei and were too smooth and too uniform in size to be nuclear lobes of fragmented pus cells. They took a deeper hemotoxylin stain than tissue cell nuclei, and appeared more homogeneous in consistency as a coccus, or slightly shaded on one side, while to light they were more refractile. That these spores are different

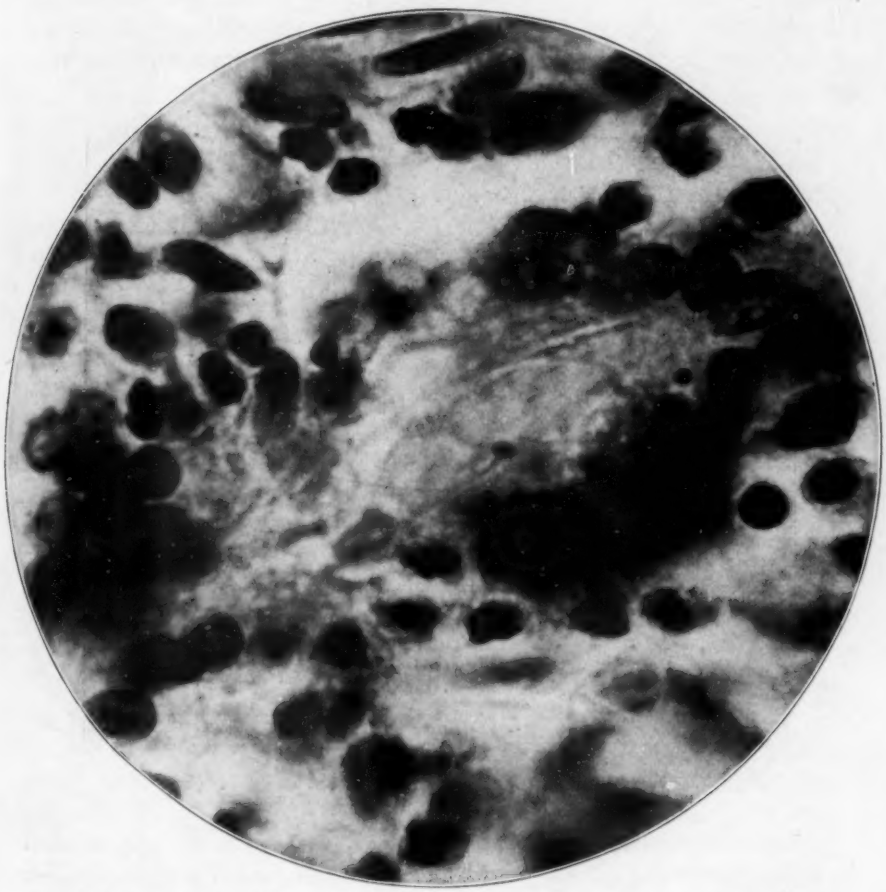

Fig. 13.—Same as figure 12, showing large giant cell with two spores.

reproductive forms from conidia is certain, for the aspergilli do not reproduce in tissue with conidial formation. The conidia seen in stained cultures differed, furthermore, in that they remained green and appeared more granular and darker in the center than at the periphery.

TREATMENT

So far no therapy has been suggested which has proved to be adequate for the cure of this disease even though a few isolated instances

have been cited in which cures apparently have been effected by various chemical preparations. That such treatment alone is unsatisfactory is suggested by the variety of remedies recommended, such as preparations of copper,[14] mercury,[15] arsenic, bismuth, boron, iodine [16] and thymol for systemic administration rather than local application. Chemotherapy alone in our hands was inadequate to effect a cure. The local application of essential oils as suggested by Myers [17] for other types of fungus infection, although irritating, seemed to check somewhat the extension of the disease. Iodoform, however, was not irritating while it was equally effective.

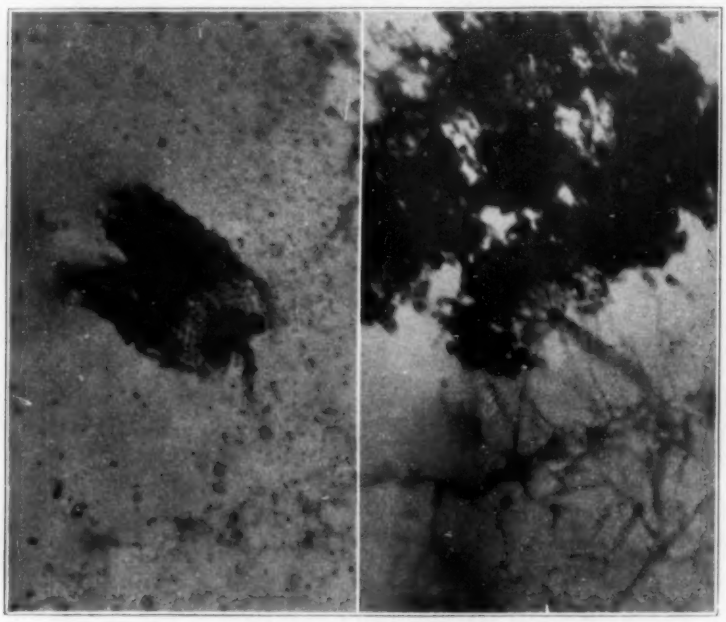

Fig. 14.—Aspergillus nidulans cultured from a grain (10×45).

Because various preparations of iodine have long been recommended in different fungus diseases, it should be noted that neither potassium iodide given by mouth in huge doses to more than 1,000 grains (65 Gm.) a day for over a month, nor the repeated intravenous use of a compound

14. Palmer, F. J.: A Case of Madura Foot Treated by Chemotherapy; Apparent Cure, Indian M. Gaz. **61**:74, 1926.

15. Audrain, L. C.: A Case of Mycetoma, J. A. M. A. **83**:1165 (Oct. 11) 1924.

16. Woolrabe, Frederick: Curability of Madura Foot, J. Trop. Med. **21**:146, 1918.

17. Myers, H. B., and Thienes, C. H.: The Fungicidal Activity of Certain Volatile Oils and Stearoptens, J. A. M. A. **84**:1985 (June 27) 1925.

solution of iodine (Lugol's solution),[18] was effective in altering the course of the disease. Pinoy has felt that the edema present about foot lesions is so great that the iodide is eliminated before being able to act. Such does not seem to be the case for, about the lesions in our patients, the deformity from edema was insignificant.

Neither roentgen nor surgical therapy has been developed to produce satisfactory results. The disease continues unabated after the use of x-rays, and it recurs after excision. When an extremity has been involved, amputation has been necessary to cope with the infection.

From the studies carried out on the case reported here, it is felt that certain principles for treatment have been determined for the successful eradication of the disease.

As the disease is always localized and never systemic, and spreads only by contiguity to surrounding tissues or by reinfection, it is reasonable that the most desirable treatment should be that directed to the disease locally. The zone of invasion in the tissues surrounding the primary focus of infection is much wider in this type of infection than in the infections with schizomycetes. It is known too[19] that in wood infections with molds the hyphae burrow deeply into the wood far beyond the borders of the gross evidence of the existence of infection. The extension of the disease in the present case and its recurrence after what seemed to be adequate excision seems to indicate a similar tendency in man. Furthermore, we have seen demonstrated how this infection burrows in the subcutaneous tissue beyond the margins of the skin and under skin which appears to be normal both clinically and microscopically. Because the skin is not primarily involved, there is a tendency for it to heal and seal over infected tissue beneath. Not only must the excision include a liberal margin of healthy appearing tissue surrounding that tissue which is obviously diseased, but the margin of skin should be resected even further to leave a beveled edge and effect a saucer-like depression. The wound so produced may then be filled with iodoform and packed with iodoform gauze. The resection of an adequate margin of skin allows the granulations which are constantly covered with iodoform to fill in from the bottom before epithelization arches over from the sides. Three lesions, two in front of and above the right ear and one on the right forearm, were eradicated the first time they were treated according to this method. Because of a desire to leave as much tissue as possible behind the ear insufficient tissue was removed so that the lesion recurred until excised the third time.

18. Voizard, F., and Leroy, D.: Madura Foot Due to Madurella Mycetomi, Bull. Soc. de path. exot. **21**:511, 1928.

19. Richards, C. H.: Personal communication from the Forest Products Service of the United States Department of Agriculture.

No recurrence has developed on the forearm in over three years, while about the ear there has been no recurrence for one year.

SUMMARY

A case of maduromycosis with black grains due to *Aspergillus nidulans* producing multiple subcutaneous lesions about the head and on one forearm is reported as occurring in a 19 year old white girl, a native of New York, in whom a cure has been effected.

BACTERICIDAL PROPERTIES OF HUMAN SWEAT*

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In a previous report it was shown that human sweat is an excellent culture medium for certain bacteria.[1]

Little work has been done on the bactericidal properties of sweat. In studying the subject of lysozyme and its presence in different tissues, Fleming and Allison[2] stated that this substance was absent in human sweat. No other reference to this subject has been found. An investigation was made, therefore, with three objects in view, namely: (1) to determine whether human sweat, sterilized by passage through the Berkefeld filter, will permit bacterial growth; (2) if it does, to determine the presence or absence of bactericidal substances in it, and (3) to note the influence of pyogenic skin infections on bacterial growth.

METHOD OF INVESTIGATION

The subjects in whom sweating was induced were patients selected from the dermatologic clinic of the Montreal General Hospital.

The procedure for the collection of sweat was that previously described.[3] No consideration was paid to the intake of food or of fluid. It was essential that medication was not applied to the skin for a few days before sweating was induced.

The specimens of sweat were slightly turbid from the admixture of dirt and epithelial débris. These were cleared in the usual manner through filter paper.

Sterilization was obtained by filtration of the material through a Berkefeld filter. Portions of this filtrate were then inactivated in the hot water bath for one-half hour at 55 C. Further portions were sterilized in the autoclave for thirty minutes under 15 pounds of pressure. Both the active and the inactivated samples of filtrate were then kept in the refrigerator until required.

These studies were carried out to determine whether inactivation of sweat resulted in a disturbance of growth in that medium. It was also desired to determine whether sweat depended, as a culture medium, on the condition of the skin at the time sweating was induced. It was felt that this could best be done by comparing the growth of the organism in each with its growth in a standard control culture medium. The medium adopted as a control was standard nutrient broth, with the addition of 0.5 per cent of dextrose.

A strain of *Staphylococcus pyogenes-aureus* obtained from a patient with dyshidrosis of the palms was used throughout. In all experiments, a twenty-four

* Submitted for publication, June 15, 1929.

* From the Departments of Dermatology and Pathology, the Montreal General Hospital.

1. Usher, B.: Human Sweat as a Culture Medium for Bacteria: Preliminary Report, Arch. Dermat. & Syph. **18**:276 (Aug.) 1928.

2. Fleming, A., and Allison, V. D.: Brit. J. Exper. Path. **3**:252 (Oct.) 1922.

3. Usher, B., and Rabinowitch, I. M.: Excretion of Sugar in Sweat: Its Relationship to Eczema, Arch. Dermat. & Syph. **16**:706 (Dec.) 1927.

hour culture in broth was used. One loopful of a moderately cloudy suspension was added to 3 cc. of the control medium, the Berkefeld-filtered sweat and the inactivated Berkefeld-filtered sweat. The cultures were then incubated at 37 C. At intervals of fifteen, twenty-four and forty-eight hours, bacterial counts were made of each. This was done by the addition of one loopful of each culture to 10 cc. of phys.ologic solution of sodium chloride and mixing thoroughly. One-tenth cubic centimeter of each of these was added to melted agar, mixed and the mixtures poured into Petri dishes. After incubation for twenty-four hours, the colonies were counted.

Growth in the various specimens of sweat was estimated as a percentage of that in the control, that in the control being considered as 100 per cent.

Similar experiments were carried out with a strain of *Cryptococcus*, which Dr. Cleveland White of Chicago sent me. This organism was obtained from the forearm of a child with dermatitis, and was found to be pathogenic for that patient.

In all instances, a seventy-two hour suspension of this organism was used.

RESULTS

The staphylococcus grew well in all the specimens of sweat.

For the first twenty-four hours, growth in the Berkefeld filtrate was somewhat less than that in the standard medium. At fifteen hours, growth in the former was 65 per cent that in the control; at twenty-four hours, it was 75 per cent. At the forty-eight hour interval, however, growth in the sweat was much more luxuriant, being 151 per cent of that in the broth. After from several days to a week, the growth in both became equal.

Growth in the inactivated sweat differed somewhat from that referred to in the foregoing paragraph. At the fifteen hour interval, growth in this medium was 77 per cent of that in the broth; at twenty-four hours, 75 per cent, and at forty-eight hours, 87 per cent. At all times, growth was less than in the broth. Table 1 details the observations mentioned.

In the comparison of the growth in the active Berkefeld filtrate with that in the inactivated filtrate, it will be noted that at the twenty-four hour interval the observations were the same. At the end of fifteen hours, growth in the inactivated Berkefeld filtrate was 18 per cent greater than that in the Berkefeld filtrate. At the end of forty-eight hours, growth in the former was 42 per cent less than that in the latter.

Bacterial counts were similarly made in three samples of sterilized sweat filtrate inoculated previously with the organism. These counts were essentially the same as in the inactivated samples of sweat.

The presence of pyogenic infection on the skin did not appear materially to affect the observations given. Independent of the presence or absence of disease of the skin, growth of *Staphylococcus pyogenes-aureus* in the first twelve hours appeared to be more luxuriant in the inactivated sweat. Growth in the unchanged sweat, however, soon outstripped that in the inactivated specimens. It will be noted, however,

that the presence of pyogenic infection resulted in a sweat medium in which growth of the staphylococcus was less luxuriant than that in the sweat from a normal skin. The results are detailed in table 2.

It is possible that immune substances may be adsorbed to the filter in passage of the sweat through it. It has been shown, however, that this will occur when only small amounts of the material are used. In the course of the experiments, no correlation was noted between the volume of sweat filtered and the bacterial growth in it.

The cryptococcus was found to grow equally well in eight specimens of sweat. Counts, however, were not made of the sweat cultures of

TABLE 1.—*Growth of Staphylococcus Pyogenes Aureus in Sweat; Estimated as Percentages of Growth in Dextrose Broth*

	Berkefeld Filtered Sweat			Inactivated Berkefeld Filtered Sweat		
	Bacterial Counts At			Bacterial Counts At		
Condition of Skin	15 Hours	24 Hours	48 Hours	15 Hours	24 Hours	48 Hours
Normal	100	110	180	160	150	100
Normal	50	70	250	100	100	160
Normal	66	67	90	85	81	80
Psoriasis	56	54	250	60	40	136
Neurodermite	180	200	220	100	160	180
Dermatitis on hands	50	...	200	70	...	100
Generalized ecthyma	35	36	90	45	35	48
Furunculosis on body	55	60	90	80	45	50
Furunculosis on axillae and acne	20	30	40	15	12	10
Sycosis barbae	22	12	42	20	11	28
Average	65	75	151	77	75	87

TABLE 2.—*Influence of Pyogenic Infections on Growth of Staphylococcus Pyogenes-Aureus in Sweat; Estimated as Percentages of Growth in Dextrose Broth*

		Berkefeld Filtered Sweat			Inactivated Berkefeld Filtered Sweat		
		Bacterial Counts At			Bacterial Counts At		
Condition of Skin	Number of Patients	15 Hours	24 Hours	48 Hours	15 Hours	24 Hours	48 Hours
Pyogenic infections	5	37	34	93	46	33	47
Nonpyogenic infections	5	86	100	218	101	106	132

this organism. Comparative estimation of its growth in the various samples revealed approximately equal growth. Inactivation or sterilization resulted in no noticeable alteration in the sweat as a culture medium for the cryptococcus.

COMMENT

It may be concluded from the observations made that human sweat sterilized so as to preserve any bactericidal substances that may be present is an excellent culture medium for *Staphylococcus pyogenes-aureus* and *Cryptococcus*. It may also be concluded that that secretion does not cause complete inhibition of the growth of these organisms. It is possible, however, to state that human sweat is slightly bactericidal to

Staphylococcus pyogenes-aureus. There is definite inhibition of growth in the first twenty-four hours; this inhibition, however, soon wears off. The presence of pyogenic skin infections does not appear to increase the bactericidal properties of sweat, although the series is too small to permit one to draw definite conclusions.

These observations may be construed differently. Brann [4] recently showed that the epidermis is bactericidal to *Staphylococcus pyogenes-aureus*. He has also shown that this inhibitory substance is easily extracted, even with distilled water. When sweating is induced, there is always an admixture of epithelial débris. Because the inhibition to the growth of the staphylococcus, detailed in the experiments reported, is so slight, it is felt that whatever bactericidal properties are possessed by sweat may be derived from the epithelial débris. It must be concluded, therefore, that human sweat has not yet been shown to be bactericidal to *Staphylococcus pyogenes-aureus* or to the cryptococcus.

4. Brann, G.: Klin. Wchnschr. **43**:2059 (Oct. 21) 1928.

HYPERSENSITIVENESS TO ARSPHENAMINE IN GUINEA-PIGS

I. EXPERIMENTS IN PREVENTION AND IN DESENSITIZATION *

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In a recent paper W. Frei [1] reported that he had been able to sensitize the skin of guinea-pigs by means of a single intradermal injection of a small quantity of neoarsphenamine. This sensitization could be demonstrated later by the changed reaction of the skin to a second injection of the same substance.

Although some other successful sensitizations of animals to chemically defined substances have been reported in the literature, the experiments of Frei offer a skin hypersensitivity in animals which fulfils an unusually large number of the requirements for experimental research. To my mind, they give a method of investigating processes of hypersensitivity which embodies the following advantages: 1. The substance employed is one which plays an important rôle in conditions of hypersensitivity in human beings (arsphenamine dermatitides) which have already been studied both clinically and experimentally (Klauder,[2] Kagelmann,[3] Biberstein,[4] Frei and Mayer,[5] Frei,[6] Stauffer,[7] Nathan and Munk,[8] and many others [9]). 2. The test object is the guinea-pig, from many points of view the ideal experimental animal. 3. The method and technic of sensitization are extremely simple. A single intradermal injection suffices. 4. The testing of the state of sensitivity can be

* Submitted for publication, May 24, 1929.

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1. Frei, W.: Klin. Wchnschr. **22**:1026, 1928.

2. Klauder: Arch. f. Dermat. u. Syph. **5**:486, 1922; Zentralbl. f. Haut- u. Geschlechtskr. **15**:105, 1925.

3. Kagelmann: Zentralbl. f. Dermat. u. Syph. **19**:203, 1926; ibid. **22**: 622, 1927; Arch. f. Dermat. u. Syph. **153**:173, 1927.

4. Biberstein: Beiträge zur passiven Uebertragung der Ueberempfindlichkeit gegen chemisch bekannte Stoffe, Jena, Gustav Fischer, 1920; Klin. Wchnschr. **3**:99, 1929.

5. Frei, W., and Mayer, R.: Arch. f. Dermat. u. Syph. **153**:606, 1927.

6. Frei, W.: Klin. Wchnschr. **12**:534, 1928; footnote 1.

7. Stauffer, Hans: Schweiz. med. Wchnschr. **43**:8, 1928.

8. Nathan and Munk: Klin. Wchnschr. **24**:1125, 1928; Dermat. Wchnschr. **20**:678, 1928; Arb. a. d. Staats Inst. f. exper. Therap. **21**:298, 1928.

9. Kerl: Jadassohn's Handbuch, Berlin, Julius Springer, 1928, vol. 18, pp. 613, 615, 618, 628 and following.

accomplished by the same simple method, and the test reaction is a visible process in the skin. 5. The sensitization occurs regularly both in regard to the incubation period and the duration of the reaction. 6. Under given conditions a high percentage (almost 100 per cent) of positive sensitizations can be obtained. 7. The last and perhaps most important advantage is that the material employed is not a complex mixture of known and unknown substances, as in the case of serums, pollens, bacterial products, etc., but, at least at the time of its introduction into the animal organism, an aqueous solution of a chemically known and defined synthetic substance, which can be easily prepared and can be applied with quantitative exactness and uniformity.

While the other sensitizations which have been achieved in animals may offer one or several of these advantages, no other method of sensitization exists as yet in which the combination and sum of factors is so favorable. It is superfluous to go into details concerning previously reported sensitizations to arsphenamine and related substances, as Frei [1] in his paper gave a short review and critical analysis of the various experiments and their results.

Since Frei's report, however, certain new facts have appeared concerning one of the experimental sensitizations that he referred to. These impel me to the following remark. The reported sensitizations of animals to nickel sulphate (Walthard [10]) are, as far as I can see, the only successful skin sensitizations of animals to a known chemical substance not belonging to the arsphenamine group. Certain special circumstances which have not been further investigated must be at play in sensitizations to nickel; for in contradistinction to the observations of Schittenhelm and Stockinger [11] in nickelplaters in Kiel (100 per cent became hypersensitive) Werner Jadassohn and Fritz Schaaf [12] reported that such sensitizations hardly ever occur in nickelplaters in the Swiss factories, and that they were unable to sensitize human beings experimentally with solutions of nickel sulphate, although they employed the same technic used by Walthard in guinea-pigs. Furthermore, Coca [13] reported that he and E. L. Milford were unsuccessful in sensitizing guinea-pigs to nickel chloride, even though they employed repeated applications on previously traumatized skin.

On account of the advantages already outlined, I believe that the intradermal sensitization of guinea-pigs to neoarsphenamine enables one to avoid many of the difficulties which previous investigators have

10. Walthard: Schweiz. med. Wchnschr. **56**:603, 1926.

11. Schittenhelm and Stockinger: Ztschr. f. d. ges. exper. Med. **45**:68, 1925.

12. Jadassohn, Werner; and Schaaf, Fritz: Arch. f. Dermat. u. Syph., to be published.

13. Coca, A.: The Newer Knowledge of Bacteriology and Immunology, University of Chicago Press, 1927-1928, p. 1014.

encountered through the employment of other methods and substances. It is therefore possible that the use of this new method may prove of value in studying the many general theoretical and practical problems awaiting solution in the entire group of diseases and conditions attributable to hypersensitivity. While the method can and should be employed in the study of such general questions, it is particularly fitted for the investigation of all toxicodermas, especially drug eruptions. For all these reasons, I performed a series of experiments in hypersensitiveness of guinea-pigs to neoarsphenamine, some of which were briefly described in a preliminary report.[14]

Before giving a more detailed account of these and subsequent experiments individually, I should like to give a description of the general technic employed in the entire series.

TECHNIC

In the main, the technic and method were identical with those of Frei.[9] They were varied only when the question involved in the particular experiment demanded a change.

Healthy guinea-pigs weighing from 180 to 250 Gm. each were employed. In most cases, I selected animals with white flanks in order that the skin reactions could be accurately observed on the unpigmented skin. There were also a few albinos among the animals.[15]

The substance used for sensitization was ordinary neoarsphenamine (in the following report the name arsphenamine will also be used to designate this substance).

For intradermal injections the solution was prepared by first dissolving 0.15 Gm. of neoarsphenamine in 10 cc. of distilled water and adding 90 cc. of a physiologic solution of sodium chloride. Both for preparation and testing, 0.1 cc. of this solution was employed. This amount contains 0.00015 Gm. of arsphenamine.

Only freshly prepared solutions were used, and these were discarded as soon as they showed definite signs of oxidation or clouding. Some time (twenty-four hours, whenever possible) before each intradermal injection and before each experiment involving examination of the skin (for dermatitis, generalized exanthemas, etc.), the flanks of the animals were lathered with ordinary unscented shaving soap and were shaved with a sharp razor. This was done with great care to avoid cutting, scraping or otherwise injuring the skin during the process. No depilatories were used.

In the case of intracardial injections, a more concentrated solution of arsphenamine was employed: 0.3 Gm. of neoarsphenamine was dissolved in 15.0 cc. of distilled water. One cubic centimeter of this solution contains 0.02 Gm. of arsphenamine and represents the amount which Frei found to be about the minimal lethal dose for guinea-pigs of the weight used. This solution was injected

14. Sulzberger, Marion B.: Klin. Wchnschr. **8**:253, 1929.

15. Although the number of albinos was too small for me to venture a definite statement, it seemed that these animals were somewhat more easily sensitized and reached a higher degree of hypersensitivity than the general run of strongly pigmented guinea-pigs (compare Hanawa: Dermat. Ztschr. **20**:761, 1913).

intracardially in quantities varying from one-third to three-fifths of 1 cc. (i.e., from one-third to three-fifths of the minimal lethal dose).

The injections were carried out with the greatest exactitude and uniformity possible. For an intracardial injection, the solution was brought to approximately body temperature. After the needle had entered the heart a considerable quantity of blood was first aspirated. The mixture then was injected so slowly that approximately forty seconds were needed to empty the syringe.

In the intramuscular, intrapleural and other internal injections, it was particularly necessary to avoid bringing any of the solution into the skin itself. In order to accomplish this, a new sterile needle, which had not been used for previous injections of arsphenamine, was thrust through the skin and its point was brought into the organ or cavity that was to receive the injection. Only after this had been done was the syringe containing arsphenamine affixed to the needle and the injection made. Great care was taken in withdrawing the needle, this being done quickly and cleanly; the deeper tissues about the needle were compressed so that any vestiges of arsphenamine should be wiped away before the point again passed through the skin.

The intradermal injections, on the other hand, were performed so that the entire amount of solution was injected into the skin as superficially as possible.

In tests made with vital stains, histologic examination showed that with the technic employed, most of the solution was brought immediately beneath the epidermis and that small quantities were even conveyed into the epithelium itself.

Each series of injections, whether administered intradermally, intracardially or otherwise, was controlled by injecting the solution into a number of normal animals besides those mentioned in the protocols.

PROBLEMS INVESTIGATED

The first problems that were investigated and the experiments that I wish to describe in this paper dealt with the questions of prophylaxis (i. e., the prevention of sensitization) and desensitization.

These two processes are obviously of the greatest practical importance; yet knowledge seems to have advanced little further in their actual application in the treatment and prophylaxis of various skin diseases than at the time when J. Jadassohn [16] first pointed out the possible pathogenetic significance of idiosyncratic reactions and mechanisms of hypersensitivity in eczemas (of course, occupational dermatitides are included in this term), and discussed these mechanisms and their significance in urticaria and toxicodermas, including drug eruptions. I wish to avoid a misunderstanding on this point, and therefore emphasize that the foregoing remark applies only to skin diseases, and does not include, for instance, allergic asthma and hay-fever. Due to the excellent work of Coca,[17] Cooke, Grove, Spain, Walzer, Parker, Stoorm van Leuwen and Hansen (to name only a few who have worked in this

16. Jadassohn, J.: Verhandl. d. V. deutsch. dermat. Gesellsch. Graz, 1895; Quatrième Congrès internat. de dermat. et syph., Paris, 1900, p. 33; Die Deutsche Klinik am Eingang des 20 Jahrh., 1905, p. 20; Klin. Wchnschr. **2**:1680, 1923.

17. Coca, in Tice: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, 1920.

field), if one can judge by the literature, the practical value of specific desensitization and prevention of sensitization has been established, to a certain degree, in both the diseases mentioned.

Even in skin diseases specific desensitizations have been used effectively in some cases, most successfully perhaps in Rhus dermatitis (Strickler,[18] Schamberg,[19] Williams, McNair,[20] Biberstein,[21] etc.). As early as 1895, J. Jadassohn,[22] who first attacked this problem in toxicodermas (drug eruptions), Galewsky [23] and others reported successful specific desensitizations with mercury, which, at that time, were naturally of greatest practical importance. Other specific desensitizations of allergic toxicodermas have been achieved with chrysarobin, potassium iodide and other drugs. The fact that persons who are repeatedly treated with ultraviolet rays after a while no longer react with inflammation, may perhaps also be classed with the specific desensitizations, although the recent experiments of Miescher [24] seem to show that the desensitization is simply due, in a great degree, to the development of a thicker stratum corneum.

In spite of these facts, practical employment of these processes is still extremely limited, especially in arsphenamine dermatitis as well as in occupational dermatitides and eczemas. It is in these diseases that the need for a practical means of combating sensitization is most urgent. I feel justified in making this statement, although even in these last named diseases successful desensitizations, both specific and nonspecific, have also been reported in many cases; for it is necessary, at present, to regard these as exceptions. Perhaps future systematic and careful attempts to desensitize a great number of patients suffering from eczema and dermatitis, combined with experimental research in this direction, may lead to the discovery of a method which will change this fact, and desensitizations may then become the rule in these conditions. At this stage, however, the process is so uncertain in result and at the best requires such a great amount of the time of both physician and patient that in most cases one is forced to resort to other means. While it is recognized that the ideal method would be permanent desensitization of each patient, one must generally be satisfied with symptomatic treat-

18. Strickler, Albert: Zentralbl. f. Haut- u. Geschlechtskr., 1924, p. 58; Studies Concerning Influence of Arsenical Preparations on Cutaneous Tests, Arch. Dermat. & Syph. **4**:177 (Aug.) 1921.

19. Schamberg, J. F.: Desensitization of Persons Against Ivy Poison, J. A. M. A. **73**:1213 (Oct. 18) 1919.

20. McNair, J. B.: Pathology of Rhus Dermatitis, Arch. Dermat. & Syph. **3**:383 (April) 1921; Rhus Dermatitis, Chicago, University of Chicago Press, 1923.

21. Biberstein (footnote 4, second reference).

22. Jadassohn (footnote 16, first reference).

23. Galewsky: Verhandl. d. V. deutsch. dermat. Gesellsch. Graz, 1895.

24. Miescher: Klin. Wchnschr. **18**:840, 1929.

ment, plus (in eczemas, etc.) the discovery and removal of the causative agent or agents. The tracing of such agents may require a great deal of time and detective work or may even be impossible. In this last eventuality, nonspecific desensitization would be the only fully satisfactory therapy. It is even probable that a great part of the counter-irritant treatment for eczemas, etc. (with tar, salicylic acid and chrysarobin), is based on a not sufficiently recognized and systematized process of nonspecific desensitization.

In the case of arsphenamine dermatitis, the substance to blame is always known. One is here confronted especially with the question of possible specific desensitization. This is also of the utmost practical importance, as in many cases the syphilis of the patient demands further intensive treatment with arsphenamine. Stokes [25] called attention to this fact in dealing with complications from the use of arsphenamine, and in the Mayo Clinic even employed a method (Besredka) which may be regarded as a form of desensitization (intravenous injection preceded by administration of one tenth of the total amount, by the same route, one hour previously).

While the experiments reported concern these questions of desensitization and prevention of the occurrence of hypersensitive states, and may perhaps point a way for the further investigation of these problems, they are only a beginning and the conclusions reached can only be applied with the greatest caution to the therapeutic measures.

EXPERIMENT 1

Twenty-five guinea-pigs were given intradermal injections, in the left flank, of 0.1 cc. of the solution of arsphenamine described. Twenty-four hours after the intradermal injection, six of the animals (nos. 122, 123, 124, 125, 126 and 127) each received an intracardial injection of 0.3 cc. of a solution of 0.3 Gm. arsphenamine in 15 cc. distilled water. Although this injection represents about one third of the lethal dose, it caused no ill effects other than quickly passing signs of shock in a few of the animals.

Within twenty-four hours after injection, a small, slightly reddened papule appeared. This marked the site of injection from one to two days in almost all cases and then gradually disappeared. Only exceptionally could I observe a slight redness and swelling that persisted for a longer period.

Six days after the intradermal injection, some of the animals that were not treated intracardially began to show a flare-up of the area in which the injection was made (nos. 130, 131, 132, 134, 137, 139 and 149 in fig. 1). At this time the site of the injection began to swell again and a marked redness once more made its appearance. Both swelling and redness increased in the days following (fig. 1) until a papule varying in size from that of a lentil to that of a large pea was formed. In some cases the center of the larger papules became necrotic. Not only did the strength of the reaction increase from day to day but the number

25. Stokes, John H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1927, pp. 289 to 337.

of animals in which the flare-up took place grew daily larger. While on the sixth day after intradermal preparation only seven of the nineteen animals not treated intracardially showed signs of reaction, on the fifteenth day sixteen of the nineteen gave positive reactions, only animals 150, 151 and 154 (fig. 1) giving negative results. On the nineteenth day, guinea-pig 154 was tested by an intradermal injection into the right flank and showed what may be called "the reaction of hypersensitivity." Thus, on the twentieth day, seventeen of the nineteen guinea-pigs showed apparent hypersensitivity of the skin.

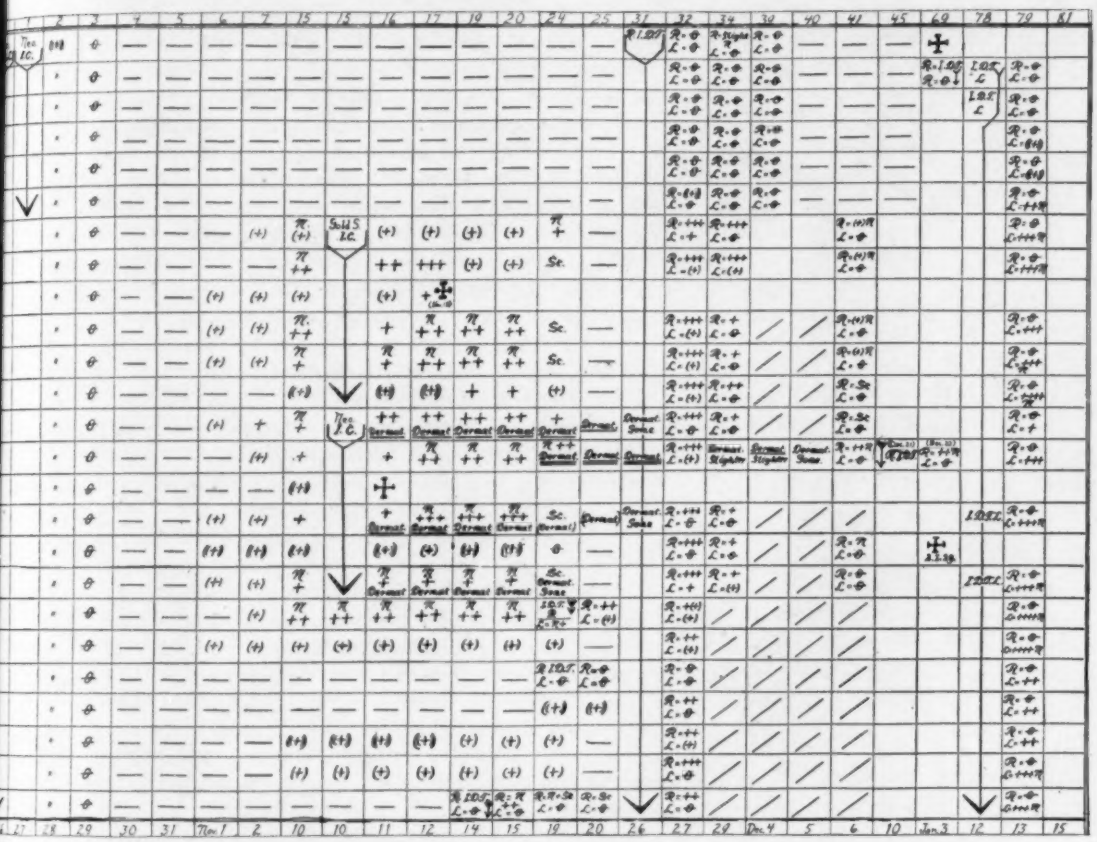

Fig. 1.—The figures of the first row represent the number of days after the first injection. The extent of the reaction is represented as follows: ((+)) the size of a small lentil, (+) of one-fourth pea; + of one-half pea, ++ of a pea, and +++ of a bean; ++++ spreading over most of the flank; θ no reaction; — reaction unchanged since previous reading, and / reaction not controlled on that day. *L* indicates the left flank, *R*, the right flank; *Dermat.*, a slight dermatitis, marked dermatitis (underlined once) and strong dermatitis (underlined twice; *Sc*, scar; *N*, necrosis; *Neo.*, neoarsphenamine; *Gold S.*, gold salts; *I. D.*, intradermal injection; *I. C.*, intracardial injection, and *I. D. T.*, intradermal test injection of neoarsphenamine. The arrow represents the injections, and the cross, death from an intercurrent cause.

Both this gradual increase in the number of animals becoming hypersensitive and the gradual increase in the strength of the reaction in the individual animals are noteworthy. They are important for a conception of the course and nature of the hypersensitivity.[26]

The observations in the six guinea-pigs nos. 122, 123, 124, 125, 126 and 127) which received intracardial injections of arsphenamine in the first twenty-four hours after preparation, stand in marked contrast to that occurring in the other animals.

In all the animals used in this experiment the small primary papule appeared at the site of intradermal injection within the first twenty-four hours and disappeared after about two days. After the disappearance of this papule, however, and from this time on, the course of the reaction in the first six guinea-pigs differed entirely from that of the others. The site of injection in guinea-pigs 122, 123, 124, 125, 126 and 127 remained without signs of inflammation. After the first few days, and during the entire period of observation, the site of that injection could scarcely be distinguished from the normal skin. In other words, the flare-up of the site of injection which took place in fifteen of seventeen[27] of the other animals did not occur in any of the six guinea-pigs which had received arsphenamine intracardially twenty-four hours after the first intradermal injection.

Thirty-one days after the first injection the state of hypersensitivity of the entire series was tested by a second intradermal administration of arsphenamine. The injection was exactly the same as the first in quantity, concentration, etc., but was given into the right instead of into the left flank. At this time only twenty-three guinea-pigs remained in the experiment, animals 130 and 136 having died of intercurrent disease. Of the seventeen animals that had not received intracardial injections of arsphenamine twenty-four hours after the sensitizing treatment, sixteen showed the "reaction of hypersensitivity." Of this group, only guinea-pig 150 manifested no reaction of this kind, but responded with a small, scarcely visible papule. Figure 1 shows that this guinea-pig was also among those which did not flare up.

The reaction of hypersensitivity to the second intradermal injection was radically different from the described reactions in guinea-pigs that received arsphenamine for the first time. The reaction which appears in normal guinea-pigs from twenty-four to forty-eight hours after the first injection is slight and obviously different from the considerable inflammatory process which developed in the same length of time as a result of the second injection. Comparison of the small papule which is formed after the first injection with the large violently inflamed and infiltrated area which now appeared proved that a definite change in reaction, a sensitization of the skin, had taken place.

There were also marked differences between the reaction to the second injection and the previously described spontaneous flare-up of the first site. Instead of making its appearance like the flare-up, after an interval of from six to nineteen days, the reaction of hypersensitivity at the site of the second injection

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26. Figure 1 shows that guinea-pigs 128 to 139 each received an intracardial injection on the fifteenth day after intradermal preparation. This was done for the purpose explained in experiment 2. The intracardial treatment evidently did not influence the subsequent reaction of these animals to intradermal injections of arsphenamine, and these twelve animals continued to respond to the injections in the same manner as the seven controls not treated intracardially (nos. 148 to 154, fig. 1). I therefore feel justified in further noting the entire series in this experiment.

27. These figures represent the guinea-pigs surviving on the twenty-fourth day.

developed to its full extent within the period from twenty-four to seventy-two hours, and from that time on began to regress slowly.

In addition to this more rapid development and course, the reaction now observed always greatly exceeded the flare-up in size, reaching, and in some cases even exceeding, that of a half dollar. The color of the reaction of hypersensitivity was often a lighter red than that which had been shown by the flare-up, and the inflammation was usually accompanied by more edema and much more infiltration of the deeper tissues. Sometimes almost the entire flank of the animal was acutely inflamed. While there had been little or no necrosis in the case of the first reactions, a central area of necrosis, almost pea-sized, was here the rule. This was followed by considerable scar formation, so that while the acute inflammatory signs receded rapidly, the necrosis and subsequent scar were visible for a long time. In both, course and aspect, therefore, the reaction to the second injection of arsphenamine was similar to that observed in tuberculous animals after injection of tuberculin, as well as to the reaction of animals with trichophytosis after the injection of trichophytin (Bloch,[28] Bloch and Massini[29] and others).

The reaction of sensitized guinea-pigs thus differed decidedly in both appearance and chronologic development from that caused by the same amount of arsphenamine in the skin of guinea-pigs not sensitized by previous injections. The latter developed only a small papule, which disappeared after one or two days, and a large percentage showed a later flare-up at the intradermal site.

The behavior of the group that was treated intracardially twenty-four hours after the intradermal injection stands in marked contrast to that of the animals described. Not one of the six guinea-pigs which had received this intracardial injection of asphenamine showed the reaction of hypersensitivity. The site of the second or test injection remained completely without reaction of any kind during the entire period of observation (more than eighty days). In fact, the reaction to the second intradermal injection did not even show the small papule typical of first contact with arsphenamine; this would lead one to believe that a certain degree of active immunity may have set in.

It is further noteworthy that in nine guinea-pigs of the group not treated intracardially (nos. 128, 129, 131, 132, 133, 135, 139, 140 and 149), the site of the first injection in the left flank, which had previously returned to a normal appearance, showed a strong inflammatory focal reaction when examined twenty-four hours after the test injection on the right side. This inflammatory focal reaction appeared and receded synchronously with the reaction of hypersensitivity.

At no time during observation was a focal reaction of the site of the first injection observed in guinea-pigs 122, 123, 124, 125, 126 and 127 which had received the intracardial injection. It remained without reaction also after the intradermal test.

The site of the second intradermal injection in guinea-pigs 122, 123, 124, 125, 126 and 127 was now observed daily in order to ascertain whether this second injection would sensitize, and would run a course similar to that in animals receiving arsphenamine for the first time. This was not the case; neither a flare-up of this area nor other signs of sensitization could be observed in any of these animals.

Seventy-eight days after the first intradermal injection, i.e., forty-seven days after the first test, all the surviving animals of the series were again subjected to an intradermal test, this time in the left flank. As shown in figure 1, all those formerly positive were positive to this test also; in addition, guinea-pigs 150 and

28. Bloch, B.: Arch. f. Dermat. u. Syph. **145**:45, 1924.

29. Bloch, B., and Massini: Ztschr. f. Hyg. u. Infectionskrankh. **63**:68, 1909.

127 had become hypersensitive. The reaction of animal 127 showed that the protective effect of the intracardial treatment had now ceased.[30] Only guinea-pigs 123, 124, 125 and 126 were still protected against sensitization.

To sum up: Twenty-three guinea-pigs (not including the two which died early during the experiment) were prepared by an intradermal injection of neoarsphenamine. Six of the animals received one third of the minimal lethal dose of neoarsphenamine intracardially, twenty-four hours after the intradermal injection. A skin hypersensitivity to neoarsphenamine could be observed in sixteen of the seventeen animals that received no intracardial injection of this kind. This hypersensitivity showed itself in twelve animals by a flaring up of the area of injection from six to fifteen days later, and in sixteen hypersensitive animals by a reaction of hypersensitivity to a second intradermal injection of neoarsphenamine. The second intradermal injection was administered to all the animals as a skin test thirty-one days after the first injection. In contrast to those which received no intracardial injection, the animals that had received an intracardial injection of neoarsphenamine at no time showed signs of hypersensitivity, in the form of either a flare-up or reaction of hypersensitivity to the skin test after thirty-one days.

A second intradermal test was applied to the entire series seventy-eight days after the first injection. Of the group of six animals that had received intracardial injections in the first twenty-four hours, four were still protected against sensitization and showed no reaction. One of this group died and one pregnant animal became hypersensitive at some time between the thirty-first and seventy-eighth day. This and all the remaining animals responded to the injection with typical reactions of hypersensitivity, only the four intracardially treated ones giving a negative reaction.[32]

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30. This guinea-pig (127) was found to be pregnant. While it is possible that pregnancy may have affected the course of the sensitization in this animal and caused it to differ in its skin reaction from guinea-pigs 122, 123, 124, 125 and 126, this question must be left open, pending further investigation into the processes involved. For obvious reasons, the influences of pregnancy and endocrine changes on immunologic processes cannot be further discussed here.

31. Reference deleted by author.

32. The four animals not sensitized (nos. 123, 124, 125 and 126) were tested again after 105 days, and had not become hypersensitive. I should like to add that for the purpose of controlling a subsequent experiment, I have since sensitized and intracardially treated three animals in exactly the same way as in the case of animals 122 to 127 in this experiment. The sensitization was prevented in two, just as in the six animals described, but the third guinea-pig became hypersensitive. Of course, the intracardial injection may have been inadequate, owing to faulty technic in this one case, but it is probable that this animal may simply have been an exception and proved refractory to this method of preventing sensitization. This naturally could be expected, and no 100 per cent rules can be applied to biologic observations of this sort.

Comment.—For the sake of simplicity it is advisable first to consider only those guinea-pigs not receiving the intracardial injection of arsphenamine within the first twenty-four hours. It will then be seen that the foregoing experiment fully confirms the observations and results of Frei. This group of guinea-pigs could be sensitized to arsphenamine in the manner and by the method described, and the same phenomena of sensitization could be noted. These consisted in various types of reaction, both spontaneous and as responses to later intradermal applications of arsphenamine. Both the flare-up (Aufflammungsphänomen) of the site of first injection and the reaction of hypersensitivity to the second injection could be observed. The first type of reaction took place in most of the animals (Frei's percentages were lower than mine),[33] while the second was present in all but one on testing after thirty-one days, and in all animals when they were tested for the second time after seventy-eight days. It is impossible, of course, to judge what effect the second intradermal injection may have had on the course of the sensitivity, and how the second test would have resulted had no arsphenamine been applied in the interval between it and the first injection.

Just as in Frei's animals the reaction of hypersensitivity differed greatly from the flare-up; its period of incubation was shorter, its course more rapid, and the inflammatory and destructive changes were more marked than those of the latter.

This difference in the clinical aspect and course of the two reactions was among the facts which led Frei to discuss the following possibilities: (1) that there might be two different types of hypersensitivity, each running its own chronologically independent course, and (2) that the existence of two types of reaction might be due to variations of degree occurring at different times in the course of the same hypersensitivity.

The results and the additional data of this experiment seem to favor the second hypothesis. The gradually increasing strength of the flare-up reaction and the gradual increase of the number of animals showing positive reactions seem to me and also to Frei,[34] to suggest that this is a hypersensitivity which increases in strength after the sixth day. Since the spontaneous flare-up at the site of first injection may be regarded as

33. These changes in results can be due to one or more of a multitude of factors: fodder, temperature of the stables, the race of guinea-pigs, etc. The colloidal state of the solution may have something to do with the faculty of sensitization. Through an oversight, I once attempted to sensitize a series of animals with a solution in which neoarsphenamine had been dissolved, not as usual first in 10 cc. of water and added to 90 cc. of a physiologic solution of sodium chloride, but directly in a mixture consisting of a physiologic solution and distilled water. The twelve guinea-pigs treated with this solution did not become hypersensitive.

34. Frei: Personal communication.

the result of the awakening hypersensitivity of the cells of the skin, a supposition of increasing sensitivity would explain the phenomena noted. According to the views that are held today by most authors, e. g., the explanation of the flare-up in experimental serum-sickness, etc. (Bessau [35]), the reaction that takes place between the hypersensitive cells and the small quantities of substance or substances remaining at the site of injection causes the flare-up. Thus, if the reaction is to occur, it is necessary that a sufficiently high degree of sensitivity develop quickly enough to encounter an adequate quantity of substance still at

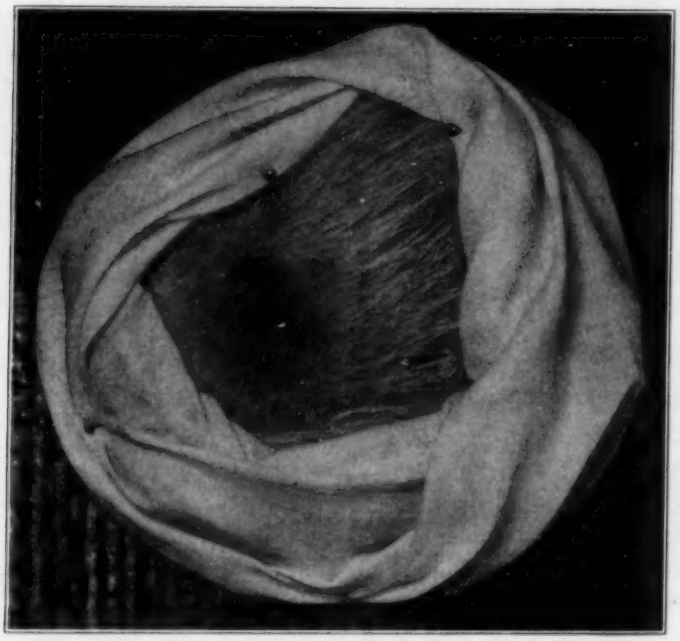

Fig. 2.—Flare-up reaction with neoarsphenamine. The site of injection thirteen days after intradermal injection of 0.1 cc. of a solution of 0.15 Gm. of neoarsphenamine in 100 cc. of distilled water.

the site of injection. This condition need not invariably be fulfilled; for instance, the speed of development of the sensitivity may not keep pace with the rate of the disappearance of the substance from the site of injection. This could be either because of a relatively too speedy disappearance of the substance or a relatively too slow development of the sensitivity. Under both conditions it is possible that a fresh introduction of a large quantity of new substance, such as is brought

35. Bessau, quoted by Biberstein and Oschinsky: Arch. f. Dermat. u. Syph. **142**:353, 1923.

about by the second intradermal injection of arsphenamine, would be capable of causing a violent reaction even in animals that had shown no signs of flare-up. It is therefore unnecessary to regard the appearance of the second reaction, even in animals that have not shown flare-up, as evidence that a new type of hypersensitivity has developed.

Further, as has already been emphasized, the reaction of hypersensitivity differed from the flare-up in its shorter incubation and course, as well as in the greater severity of its inflammatory and destructive processes. It must be borne in mind that since the work of Pirquet [36] the acceleration and intensification of a reactive process have

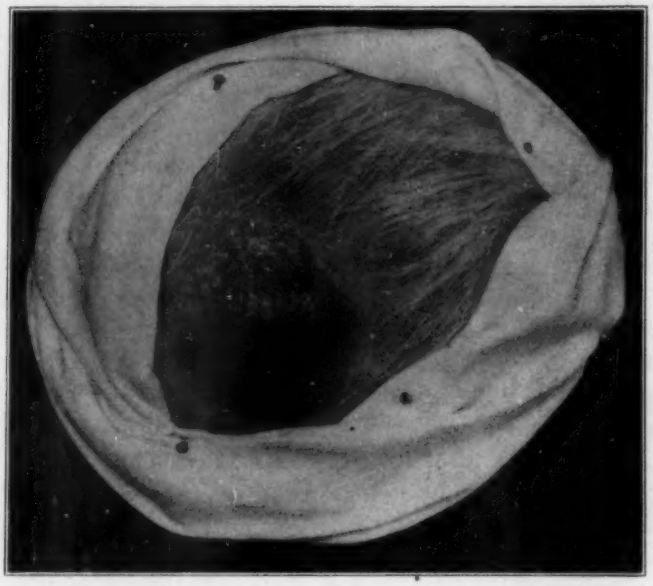

Fig. 3.—Reaction of hypersensitivity to neoarsphenamine. The site of injection, twenty-four hours after test injection. (Twenty-six days elapsed between sensitizing and test injection.)

been regarded as characteristic of the development of a high degree of hypersensitiveness in certain allergic states; therefore, either the increase of the degree of sensitivity, or the increased amount of arsphenamine deposited by the second injection, or the sum of these factors, would explain the quicker development and involution as well as the greater severity of what has been called the reaction of hypersensitivity. While all these considerations speak strongly for the probability that both types of reaction are due to variations of degree in one and the same sensitivity, the final decision of this question must be left to future

36. Pirquet: München. med. Wchnschr., 1906, p. 1457.

experiments. (Types of skin reactions in hypersensitive guinea-pigs are described by Zinsser [37] Dienes and Schoenheit,[38] and Lamson and Pope [39]).

For further discussion it will now be necessary to regard the experiment in toto, and to include the group of animals receiving the intracardial injection after twenty-four hours.

While the foregoing remarks concerning the other animals are at present only of interest in particular reference to the experiment described, the prevention of sensitization, which was achieved in guinea-pigs 122, 123, 124, 125, 126 and 127, is important for both the conception of and dealings with allergic and other processes of hypersensitiveness in general. In this last named group of animals a single intracardial injection sufficed to offset the effects of the potential sensitizing injection which had been given twenty-four hours previously. The introduction of arsphenamine into the blood stream gave all these animals an absolute protection against the employed method of skin sensitization to arsphenamine, as shown by the lack of flare-up and the negative result of the test at the end of thirty-one days. In four of them the protection was still apparent in full strength seventy-eight days after the first intradermal injection. As far as I am able to see from the accessible literature the aforementioned phenomenon is a new observation. As it was naturally impossible to investigate all the questions that have been suggested by this experiment, a definite classification of my observation among the already known forms of prevention of sensitization seems difficult for the present. An additional difficulty in an attempt at such classification is that the process of sensitization to arsphenamine is itself comparatively new, and cannot be identified with any of the other known experimental hypersensitivities in animals. Of these the hypersensitivities caused by living organisms, such as tubercle and other bacilli, bacteria and fungi, are processes whose mechanisms are for the most part still obscure and cannot be drawn into discussion here. I have already referred to the still extremely few sensitizations to chemically known substances, and to my knowledge, no successful preventions of such sensitizations have been reported.

A third form of sensitization and doubtless the one that has been studied with the greatest care and in greatest detail is the process known as anaphylaxis, which I believe unnecessary to describe here.

Without in any way assuming that the basic mechanisms of the sensitization and prevention of sensitization to arsphenamine reported

37. Zinsser, quoted by Dienes and Schoenheit (footnote 38).

38. Dienes and Schoenheit: J. Immunol. **14**:9, 1927.

39. Lamson and Pope: J. Immunol. **14**:365, 1927.

in this paper are the same as, or even closely related to, the corresponding phenomena in anaphylaxis, it is nevertheless necessary to call attention to certain outward similarities. It has been known for a long time that the hypersensitive (anaphylactic) state can be prevented or delayed in animals that have been potentially sensitized with anaphylactogens (serum, protein mixtures, complex antigens of Landsteiner, etc.). This can be done either specifically or nonspecifically; in a specific way by injections of small doses of the particular anaphylactogen during the preanaphylactic state (Doerr [40]), or by the injection of larger but sublethal doses during the anaphylactic state. The first method is more like that used in my experiment, while the latter must be considered rather as a desensitization than a prevention of sensitization. It would take me too far from my subject to discuss the various explanations for these phenomena and their relation to the prevention of sensitization to arsphenamine, it seems unnecessary to emphasize further the apparent similarities.

Certain nonspecific means of prevention of anaphylaxis have other and perhaps even greater outward resemblances to the present method of prevention of sensitization. Also, of these, only a few can be mentioned, for instance, the prevention of the onset of anaphylaxis through roentgen treatment of potentially sensitized animals, which was first reported by von Heinrich [41] in 1913. In this investigator's experiments, guinea-pigs treated with horse serum and immediately afterward with x-rays (1 Holzknecht erythema dose) did not succumb to reinjection of horse serum three weeks later; while the control animals (sensitized but not treated with x-rays) died of typical anaphylactic shock after the reinjection of the same and much smaller amounts of serum. This prophylactic effect of the x-rays had greatly diminished at the end of six weeks. The irradiation of guinea-pigs fourteen days after the sensitizing injection proved less effective in preventing anaphylaxis. Von Heinrich attributed the effect of x-rays to the influence of the rays on the lymphoid tissues (lymphoides Gewebe).

Similar experiments, in the main leading to the same results, had been performed on sensitized guinea-pigs in 1902 by Seligmann,[42] who, however, used infection with tubercle bacilli instead of x-rays.

Another, and lately much discussed, nonspecific method of preventing the development of an immunity, or hypersensitivity, is the so-called "reticulo-endothelial blockade." It must be pointed out that certain observations in this field have points of similarity with mine,

40. Doerr, R.: Verhandl. d. Gesellsch. deutsch. Naturforscher und Aerzte **47**:1018, 1924; Arch. f. Dermat. u. Syph. **151**:7, 1925.

41. Von Heinrich, Hans: Zentralbl. f. Bakt. Orig. **70**:421, 1913.

42. Seligmann: Ztschr. f. Immunitätsforsch. u. exper. Therap. **14**:419, 1920.

especially the experiments of Klinge,[43] also Schlossberger,[44] Bieling [45] and Jungeblut,[46] and their relation must be further investigated.

Only increased knowledge of the manner in which both the sensitization and prevention of sensitization to arsphenamine are obtained in the present experiment can help one to decide whether any or all of the observations in anaphylaxis, etc., described have only a superficial resemblance to the processes or whether they are due to identical or related basic mechanisms.

Practically even more important than these comparisons with other animal sensitizations is the question of the possible relationship of experimental hypersensitivity toward arsphenamine in animals and the mechanism which causes arsphenamine dermatitis and hypersensitivity in man.

The task of fitting the new phenomena observed into the scheme of the already known and classified is rendered difficult by certain large deficiencies in knowledge. For instance, as already mentioned in my preliminary report, it is even impossible to decide at present whether the result is attributable in the present case to a specific or to an nonspecific effect of the intracardial injection. The fact that prevention of sensitization to arsphenamine was obtained by injection of arsphenamine does not represent proof of specificity; the mechanism must still be studied in regard to this question. It must be determined, for instance, whether (*a*) the intracardial injection of some other substance would have served equally well in preventing sensitization to arsphenamine (related or unrelated substances could be used to determine the absolute or group specificity), and (*b*) whether the intracardial injection of arsphenamine can prevent a sensitization with and to other substances. As already mentioned, the relationship of the action of arsphenamine, which is a substance reported to effect the reticuloendothelial system, to the mechanisms of "blockade" with other substances must be particularly studied in this connection.

Besides the question of specificity of the reaction, the equally important question of locality is still unanswered. It is not yet known where the effect of the intracardial injection of arsphenamine is applied. The resulting refractory behavior of the skin in subsequent sensitizations to arsphenamine may be caused by (1) the action of the small quantities hematogenously distributed in the skin, (2) the arsphenamine affecting some other organ or organs and thus preventing the sensitization, or (3) a combination of such actions. For example, it cannot

43. Klinge, F.: Krankheitsforschung **5**:458, 1927.
44. Schlossberger, C.: Zentralbl. f. Bakt. Orig. **110**:210, 1929.
45. Bieling: Zentralbl. f. Bakt. Orig. **110**:195, 1929.
46. Jungeblut: J. Exper. Med. **45**:227, 1927, quoted by Bieling (footnote 45).

be determined whether the entire process is cellular or humoral or both, and the serologic study of the condition has not yet been attempted (precipitins, amboceptors, sensitizing antibodies, etc.).

In addition to the elucidation of the foregoing questions, quantitative studies with variations of dosage and of time intervals are necessary. Until now, arbitrarily fixed amounts and unvaried chronologic periods have been used purposely. One cannot be sure, therefore, that the optimal experimental conditions have been achieved. From the practical point of view it is especially important to ascertain what would result from the use of doses corresponding to those used in human therapy.

On account of the present ignorance of all these and other important points, I must confine myself to a statement of facts and not seek to identify or classify exactly. In spite of this, I believe that the following conclusions from this experiment are justified: The sensitization of guinea-pigs to arsphenamine is an allergic phenomenon in the sense of Pirquet's [36] original definition: "Zustandsaenderung welche der Organismus durch die Bekanntschaft mit irgend einem organischen lebenden oder leblosen Gifte erfaehrt" (change of condition which takes place in the organism through contact with an organic living or inanimate poison). From the examples then cited, it follows that Pirquet referred to specific processes.

The occurrence of this allergic condition can be prevented by an intracardial injection of the allergen twenty-four hours after the potentially sensitizing intradermal injection and the preventive power of this single intracardial injection is of long duration (more than seventy-eight days). This observation seems to be the first of its kind in allergy and further study may prove it to be of practical value.

EXPERIMENT

While experiment 1 demonstrated the successful inhibition of sensitization, the result obtained cannot be regarded as a desensitization sensu strictiori. For the word desensitization must be applied only when a certain preexisting condition of hypersensitivity is reduced in degree. Since the animals that received the intracardial injection of arsphenamine after twenty-four hours showed no manifest signs of hypersensitivity subsequent to the intradermal injection, it cannot be assumed that such a state existed. Hence it is logical to suppose that the intracardial injection did not reduce the degree of sensitivity, but prevented sensitization and the formation of the hypersensitive state. In order to ascertain whether an existing hypersensitive state could be influenced, in particular whether a desensitization could be achieved, it was necessary to experiment with animals already hypersensitive.

This was done in the following manner:

Twelve of the animals mentioned in experiment 1 (nos. 128 to 139, in fig. 1), after being intradermally prepared with neoarsphenamine in the manner described, were used in the second experiment. The exact course of the experiment is also shown in figure 1.

Fourteen days after the intradermal injection, seven of the animals (guinea-pigs nos. 129, 131, 132, 134, 135, 137 and 139) had shown to a marked degree the spontaneous flare-up of the site of injection described, which proved that they at least had now become hypersensitive. Whether or not the other five animals were already hypersensitive must be left undecided. Fourteen days after the intradermal injection, six of the twelve guinea-pigs received an intracardial injection of arsphenamine corresponding to that used in experiment 1 (0.3 cc. of a solution of 0.3 Gm. neoarsphenamine in 15 cc. distilled water). The other six animals received an equivalent intracardial injection of one third of the minimum lethal dose of gold sodium thiosulphate on the same date.

Figure 1 shows that four of the six animals receiving arsphenamine and three of those receiving gold sodium thiosulphate had shown flare-ups. As this experiment was carried out at the same time as experiment 1, the sensitization, testing, etc., were performed with the same solutions; guinea-pigs 148 to 154 served as controls for both series. All of the animals in this experiment, whether they had received intracardial injections of arsphenamine or of gold sodium thiosulphate, proved hypersensitive to arsphenamine on the application of the intradermal tests and developed a reaction of hypersensitivity to injections both thirty-one and seventy-eight days after preparation. The intracardial injection which had been administered fourteen days after the sensitizing treatment was neither specifically nor nonspecifically capable of arresting the further development of the skin hypersensitivity to arsphenamine, and the course of the process was unchanged as to the reaction of the animals to subsequent intradermal injections of this substance; no desensitization could be obtained by this method. The degree of hypersensitivity which existed in at least seven of the sensitized guinea-pigs at the time of intracardial injection was not influenced, particularly not reduced, by the introduction of arsphenamine or gold sodium thiosulphate into the blood stream. In addition to this negative result, the experiment led to the following observations.

In confirmation of the observations of Frei it was again shown that the animals sensitized intradermally to arsphenamine did not react with anaphylactic shock on intracardial injection. It is true that the time between sensitization and intracardial injection was too short for the full development of an anaphylactic state. It is perhaps necessary to add, therefore, that, in other experiments of mine which are not reported in this paper, no anaphylactic shock occurred even when the sensitizing injection and the intracardial reinjection were separated by the adequate interval of more than twenty-one days.

While neither the animals given injections of gold sodium thiosulphate nor the controls not given intracardial injections showed a reaction of the skin, a number of the other animals evidenced their skin sensitivity, exactly as in Frei's experiment, by a macular morbilliform eruption twenty-four hours after the intracardial injection of arsphenamine. The exanthems consisted of disseminated light reddish or pink, scarcely infiltrated spots, varying in size from a pinhead to a pea, and not sharply demarcated from the remaining skin. In certain parts the maculae joined to form a reddish network, so that larger and smaller areas were covered with a diffuse erythema.

In the first animal (no. 134, fig. 1), the skin was entirely covered with these spots and reddened areas. The region around the site of the old intradermal injection, the flanks which had been shaved on the previous day, the breast which had been plucked for the intracardial injection and the ear bearing the number tag were particularly strongly affected.

The second animal showing an exanthem was no. 137 (fig. 1). In this case, a morbilliform eruption of the same type appeared; it was somewhat less violent, and was confined to the areas named which had been previously shaved or irritated. In a third animal (no. 139), the eruption was even less strongly developed and appeared only in the area which immediately surrounded the place of intradermal injection in the left flank. In all three animals the site of the previous intradermal injection showed a strong focal reaction, becoming very red, inflamed and swollen twenty-four hours after the intracardial injection of arsphenamine. Both the focal reactions and the exanthems gradually regressed. At the end of five days the sites of the eruptions and reactions were covered with fine superficial scales and only slight redness remained.

While these observations, as before stated, correspond to those of Frei, a fourth animal (no. 135) developed a dermatitis of a type or a degree not previously observed. This animal, prepared and treated like the others, had shown a spontaneous flare-up of only average strength at the site of the intradermal injection. This took place between seven and fourteen days after the first injection. The intracardial injection of arsphenamine was administered, as in the other animals, on the fourteenth day after preparation. Within twenty-four hours, a slight redness and swelling at the site of the intradermal injection again appeared. This increased in degree and size during the following three days, and a small central necrosis developed. On examination, nine days after intracardial injection, the inflammation had spread and the entire skin of the animal was an angry dull red. The guinea-pig was weak and ill, and was thought moribund. The temperature was 38.8 C., measured rectally, and the blood count showed no peculiarities; there was no increase in the number of the eosinophils. The dermatitis lasted about sixteen days, being completely healed on about the twenty-fifth day after intracardial injection. On about the tenth day of eruption, the acute inflammatory symptoms began to regress, and the animal was literally covered with rather thick scarlatina-like scales. The histologic examination of the skin during the height of the disease (second day) showed the following changes:

The epidermis was widened and acanthotic, and there was some rather loosely laminated hyperkeratosis. Here and there the stratum granulosum became narrower or even disappeared; particularly in these regions there was marked intercellular and intracellular edema in the rete, with "alteration cavitaire" in the cells, and confusion and irregularity of the cell rows. The mitotic figures in the epithelium were increased in number and there were a moderate number of leukocytes in diapedesis through the epidermis. The entire picture was that of a beginning "status spongoides." In the cutis there was edema of the papillary body, and infiltration consisting mainly of leukocytes and lymphocytes, with both swelling and increase in the number of the fixed connective tissue cells. The blood capillaries appeared to be dilated. On the whole the picture is that which can be observed in an early stage of arsphenamine and other dermatitis in human beings.

The animal began to recover in strength at about the same time as the dermatitis began to regress. From then on it improved rapidly, so that after twenty-five days it was again lively and well. At this time the skin had become nearly normal in appearance and showed only small brownish spots here and there. As no his-

tologic examination was made of these spots, it is impossible to decide whether they were due to the formation of melanotic pigment or to other processes.

Of the two remaining animals that received an intracardial injection of arsphenamine on the fourteenth day, one died during the night after injection (no. 136), and the other (no. 138) showed only a slight redness as a focal reaction of the intradermal site.

To sum up: The attempt was made to desensitize twelve sensitized guinea-pigs by intracardial injections fourteen days after intradermal preparation with arsphenamine. Six of the animals received an intracardial injection of arsphenamine identical with that which had achieved the prevention of sensitization when administered after twenty-four hours in experiment 1; the other six animals received an equivalent intracardial injection of gold sodium thiosulphate. Neither of these measures was effective in desensitizing the guinea-pigs and they reacted to subsequent intradermal tests with arsphenamine fully as strongly as the sensitized but not intracardially treated controls.

The intracardial injection of arsphenamine caused no anaphylactic shock even in the cutaneously hypersensitive animals.

While the animals that had received intracardial injections of gold sodium thiosulphate showed no skin reaction, it was otherwise in the case of the six receiving intracardial injections of arsphenamine. Twenty-four hours after injection, three of the latter developed macular morbilliform exanthems of varying degrees. One of these eruptions was generalized; the other two were confined to irritated regions. Nine days after the intracardial injection of arsphenamine, a fourth animal presented an extremely severe generalized dermatitis of a type not previously described, and which clinically and histologically resembled dermatitis in human beings. In all the animals with eruptions of the skin there was also a strong focal reaction at the site of intradermal injection. The fifth guinea-pig that had received arsphenamine intracardially showed no eruption except a slight redness of the site of the previous injection. The sixth animal died during the night after the intracardial injection.

Comment.—Few words are necessary concerning the failure of desensitization in this experiment. The injection of arsphenamine after fourteen days could not influence the course of the sensitivity, at that time apparently already in full swing, whereas the same dose of arsphenamine was able to check sensitization, provided it was applied at its onset as in experiment 1. That the injection of gold sodium thiosulphate was unable to desensitize does not seem surprising and would have had a special interest only if desensitization had been achieved by the arsphenamine. This experiment simply represents an attempt with an arbitrarily chosen method, and its lack of success is not evidence that a desensitization is not impossible by other means.

What was said regarding ignorance of the process in experiment 1 holds true here as well; further, the need for chronologic and quantitative variations must be particularly emphasized.

The fact that no shock could be observed after the intracardial injection of arsphenamine confirms the conclusion of Frei that that process cannot be considered today a classic anaphylactic sensitization, although further experiments may perhaps reveal a relationship of these processes.

To my mind, the most important results obtained are the exanthematous changes in the skin observed in hypersensitive animals subsequent to the introduction of arsphenamine into the vascular system. The macular eruptions in three of the animals, which were of a different intensity in each case and appeared twenty-four hours after the intracardial injection, correspond without doubt to those observed by Frei and must also be considered experimentally achieved toxicodermas (drug eruptions) in animals. That they are a product of skin hypersensitivity to arsphenamine and the intracardial injection of arsphenamine is evidenced by the following facts: 1. The eruption appeared a short time (twenty-four hours) after intracardial treatment with arsphenamine. 2. No such exanthems were observed either in animals sensitized but not given intracardial injections, or in those intracardially injected with arsphenamine but not previously sensitized (controls) or in those sensitized with arsphenamine and intracardially treated with another substance (gold sodium thiosulphate).

The severe generalized dermatitis that was observed nine days after injection in the fourth animal was also obviously the result of the hypersensitivity plus the intracardial injection, for the focal reaction at the site of the old intradermal injection appeared twenty-four hours after intracardial injection, and the dermatitis apparently spread from this reaction. The other arguments which speak for the causal connection of the intracardial injection with this dermatitis are the same as those mentioned. One must, therefore, consider the condition of this animal as an analogon of severe arsphenamine dermatitis in human beings, to which it corresponds so far as its cause, its clinical appearance and many points in its course are concerned.

It is further interesting to note how strikingly this experiment brings out the different degrees of sensitivity in the individual animals. Five guinea-pigs of equal weight were sensitized and prepared in exactly the same manner. On the same day each received an intracardial injection of the same amount of the same solution of arsphenamine. One animal responded with the severe generalized dermatitis described, a second developed a generalized morbilliform exanthem, a third a localized exanthem of the same type, a fourth only a strong focal reaction at the sensitizing site and an exanthem of the adjoining regions of the skin,

while the fifth showed practically no skin reaction. In spite of these differences in reaction to intracardial injection all the animals reacted in approximately the same degree to subsequent intradermal tests with arsphenamine. It seems a fortunate combination of circumstances which led to such varying degrees of exanthematous reactions in this experiment. These illustrate well the individual differences in sensitivity which may be the basis of what are known as idiosyncrasies.[47] Furthermore, these differences in response of the skin of the same animal to intradermal and intracardial application of an antigen can be used as an additional argument in favor of the "quantitative hypothesis" first set up by J. Jadassohn in a case of mercury dermatitis. In this experiment, just as in Jadassohn's cases of mercury idiosyncrasy in man, there is no case in which an animal that was negative to the intradermal test showed a skin eruption on intracardial (intravenous) application, while in one case the hypersensitiveness was of a sufficient degree to give a positive reaction to the intradermal test, but not sufficient to respond with an exanthem to the hematogenous distribution. In other words, not all animals reacting positively to the concentrated application of antigen to the skin were sufficiently hypersensitive to react to the dilute antigen distributed by the blood stream, and the appearance of the skin reaction seems in some way dependent on the quantity of antigen (so-called quantitative hypothesis).

From the foregoing experiment, the following conclusions seem justified:

1. A certain quantity of arsphenamine was sufficient to prevent the development of an allergic state of the skin when injected intracardially twenty-four hours after preparation (experiment 1). This same quantity did not influence the course of the allergy in subsequent hypersensitive reactions to intradermal tests, if injected fourteen days, instead of one day, after the sensitizing injection. No desensitization could be observed as a result of this injection.

If instead of the allergen employed for sensitization (arsphenamine) an equivalent amount (one-third of the minimal lethal dose) of another substance (gold sodium thiosulphate) was injected on the fourteenth day, this was equally unable to influence the course of the hypersensitivity to arsphenamine. No nonspecific desensitization could be achieved by this method.

2. These two failures by no means prove desensitization to be an impossibility. The methods must be varied in future experiments.

3. Intracardial injections of arsphenamine administered to sensitized animals on the fourteenth day after preparation caused dermatites of

47. Bloch, B.: The Rôle of Idiosyncrasy and Allergy in Dermatology, Arch. Dermat. & Syph. **19**:175 (Feb.) 1929. Bloch, B., and Steiner-Wourlich: Arch. f. Dermat. u. Syph. **152**:283, 1926.

various degrees of severity. This fact illustrates the differences in sensitivity in individual animals and can be construed as an idiosyncratic factor. Many arguments seem to suggest that the exanthems observed are analogous to arsphenamine dermatitis in man. The particularly strong dermatitis in one of the animals was strikingly similar clinically and histologically to the severe form in human beings.

APPLICATION OF RESULTS

Before attempting to apply the results of these experiments to the actual treatment of patients, it must be borne in mind that the conditions and reactions in the experimental animal do not necessarily correspond to those in human beings. It is therefore essential to trace the analogies between the processes observed and those in man. As stated in reference to comparisons with other sensitizations in animals, this is particularly difficult on account of the newness of this experimental hypersensitivity and the few facts available. It seems, however, that there are some links which closely bind the experimental arsphenamine hypersensitiveness in guinea-pigs to analogous allergic conditions in human beings. Space and time prevent me from pointing out more than one or two general resemblances to conditions in occupational dermatitis and eczemas. In these diseases it is often the case that a more or less intimate contact with a chemical or other substance applied to a certain part of the skin results in a sensitization of the entire skin of the patient to that substance. In some cases (and perhaps a checking up on this fact would increase their number) it seems that the sensitization occurred particularly after a wound or a scratch had permitted some of the substance in question to penetrate and perhaps be deposited in the skin. It is superfluous to point out that this mode of sensitization has some resemblance to the method used in the present experiments.

The toxicoderma (drug eruption) which has the closest relationship to my experiment is arsphenamine dermatitis. It is surely beyond doubt that in man this dermatitis is due to an allergic mechanism (see J. Jadassohn [48] and Bloch [49]). This must be emphasized as a contrast to the probable pharmalogic-toxic pathogenesis in the case of some other effects of arsphenamine. This would *a priori* coincide with the present observation in arsphenamine dermatitis in animals, but does not prove that the allergic mechanisms are identical in animal and man. The facts which suggest such an identity can be divided into two groups: (1) those derived from clinical observation, and (2) those due to experiments both in animals and human beings.

48. Jadassohn (footnote 16, first, second and third references).
49. Bloch (footnotes 28 and 47).

The most important fact in the first group is one to which Klauder [2] was the first to call attention. This author pointed out that in a great many cases arsphenamine dermatitis followed an infiltration of the cutaneous and subcutaneous tissues with arsphenamine. In other words, he found that most of the cases of dermatitis occurred on the intravenous injection of arsphenamine after a paravenous injection of the same substance had occurred some time previously. Since Klauder, other authors have observed this fact. Recently, R. L. Mayer [50] reported a particularly illustrative case from the Breslau Clinic. In Mayer's case not only did a dermatitis occur, but there was a flare-up at the site of the previous paravenous injection after the intravenous administration of arsphenamine. These and similar clinical data suggest that in man just as in animals an intradermal (cutaneous or subcutaneous) depot of arsphenamine can cause a skin hypersensitivity to this substance, and that this skin hypersensitivity can manifest itself as a dermatitis on subsequent hematogenous distribution of the drug. Of course, that does not mean that all dermatitis need be attributable to just this mechanism.

The second group of facts, comprising those obtained from experiments with arsphenamine in human beings, also speaks strongly for the close relationship of these processes of hypersensitiveness in animals and in man. Klauder, Stuart and Maynard, E. Pick, S. K. Rosenthal, Frei and Mayer,[5] and others reported that patients having had arsphenamine dermatitis react to intradermal tests with arsphenamine much more strongly than normal persons. Kagelmann [8] reported the same results as these authors with intradermal tests on patients who had recovered from arsphenamine dermatitis, with the additional observation that the hypersensitiveness seemed to have an intermittent course, and that the dermatitis was followed by a period of desensitization of from nine to eleven weeks. (The latter fact was not observed in the animals of the present experiment.) Stauffer,[7] who tested several patients with arsphenamine dermatitis and a large number of normal persons by means of Jadassohn's functional skin tests (eczema tests of Bloch), found that the patients having, or having had, dermatitis gave positive eczematous reactions to various arsphenamines; he reported in addition that several "normal" persons who had never been treated with arsphenamine, also reacted positively. (Primary hypersensitivity of this sort could not be observed in any of my experimental animals.)

These observations all show that in man, just as in animals, a hypersensitivity of the skin to arsphenamine can be demonstrated in cases of arsphenamine dermatitis. Frei [51] conducted an extensive series of

50. Mayer, R. L.: Arch. f. Dermat. u. Syph. **156**:656, 1928.
51. Frei (footnote 6, first reference).

experiments on normal persons, employing for intradermal sensitization and for intradermal testing exactly the same method and the same doses of neoarsphenamine as he subsequently used in experiments on guinea-pigs. He reported that he was able to sensitize eight of sixty-six normal persons in this manner, and the sensitization demonstrated itself exactly as in animals both by a spontaneous flare-up at the site of intradermal injection and by a strong reaction of hypersensitivity to a subsequent intradermal test. Nathan and Munk [8] later reported similar results in experiments with a sulphur neoarsphenamine.

In addition, they observed two cases in which in sensitized patients a generalized urticaria followed the intradermal test within five minutes. This generalized urticarial reaction is not identical with the severe arsphenamine dermatitis of the erythematosquamous or eczematous type generally observed in human beings, which usually appears not immediately but at least twenty-four hours after the last administration of the drug.[25] Nathan and Munk, in a subsequent article, pointed out the probability that two different types of allergic mechanisms are involved. This seems even more probable when one considers that Frei and Mayer, in two cases of urticarial arsphenamine eruptions, could not obtain the reactions of hypersensitivity appearing twenty-four hours after the intradermal test with arsphenamine,[52] while this type of reaction is usually present in patients with typical severe arsphenamine dermatitis. In further support of the probability that the usual severe generalized arsphenamine dermatitides in human beings are not identical with the immediate urticarial eruptions some times observed, it seems necessary to emphasize that the urticarial eruptions in human beings are in many ways different from other types of allergic skin reactions. Two differences have been recently pointed out by Werner Jadassohn [53] and later by Stauffer.[7] 1. Patients suffering from allergic urticarias which are traceable to a certain specific agent generally give, to an application of this substance on a scratch test, an immediate reaction in the form of an urtica. If a solution of the substance is applied intradermally, a rapidly growing wheal also ensues. This form of immediate urticarial reaction need not be present in cases of allergic eczemas or nonurticarial toxicodermas. 2. The urticarial type of hypersensitivity can often be passively transmitted with the serum of the patients by the method of Prausnitz and Kuestner, while in eczematous and in other types of allergic skin manifestations (that do not show the immediate wheal reaction described), this is not possible, as a rule. The cases of toxicodermas which had been passively transmitted by the method of

52. One case was reported in a personal communication.

53. Jadassohn, Werner: Klin. Wchnschr. **5**:1957, 1926; Schweiz. med. Wchnschr. **36**:868, 1927.

Prausnitz and Kuestner (Biberstein,[54] Perutz, Lang and Der, and others[55]) may have been combinations of urticarial and other types of hypersensitiveness. This possibility cannot be excluded in these cases, as one often finds an urticarial and another hypersensitivity, for instance an erythematosquamous or an eczematous, combined in one and the same patient, whereby only one type may become manifest clinically, while the other remains masked or latent until it is demonstrated by the appropriate test. It cannot be decided whether this was true in the foregoing cases, as the toxicodermas transmitted passively by these authors were not tested to ascertain whether they reacted with an immediate urticarial wheal to the application of the drug.

The severe forms of generalized arsphenamine dermatitides do not appear as urticaria immediately after the administration of arsphenamine, and are not generally transmissible by the method of Prausnitz and Kuestner. They therefore do not seem to be identical with the usual urticarial hypersensitiveness in human beings, and probably not with the generalized urticarias after tests with sulphur neoarsphenamine, which were observed by Nathan and Munk. It must be further investigated whether the eczematous forms of arsphenamine dermatitis react with an immediate urticarial reaction or not. The few subjects that I have been able to test did not give this reaction.

That the arsphenamine dermatitis in the present experiments is closely related in its mechanism to the usual form of severe dermatitis in human beings seems highly probable when one considers that they have the following features in common: 1. They are both allergic mechanisms. 2. In certain cases the clinically observed pathogenetic mechanism in man (infiltration through paravenous injection, and appearance of dermatitis after subsequent intravenous administration) is analogous to the experimental mechanism in animals. 3. Experimental skin sensitizations to arsphenamine can be achieved by one and the same method in man and in animals and have similarities (length of incubation period, course, flare-up, focal reactions, etc.), which seem beyond those attributable to chance. 4. A skin hypersensitivity of the same type is associated with the dermatitis in both animals and man and can be demonstrated in the same way in both; namely, by a reaction of hypersensitivity to intradermal tests with arsphenamine. 5. The experimental dermatitis in animals and the dermatitis in man have great similarities in the period of incubation, in appearance and in course (Stokes[25] and Kerl[9]).

In addition to these analogies in the mechanisms of sensitization to arsphenamine, certain observations in man may perhaps be compared

54. Biberstein (footnote 4, first reference).

55. Low, R. Cranston: Anaphylaxis and Sensitization, Edinburgh.

with prevention of sensitization reported in experiment 1. While Frei achieved sensitizations to arsphenamine in eight of sixty-six normal persons (patients not under treatment with arsphenamine), he was unable to sensitize a single syphilitic patient who was being treated intravenously with arsphenamine, although he attempted to do so in seventy-seven cases.

As it has been shown in experiment 1, that a long-lasting prevention of sensitization can be achieved in guinea-pigs by a single intracardial injection of arsphenamine, it is conceivable that Frei's failures in sensitization of man can be attributed to intravenous injections of arsphenamine. It is possible that the injections in human beings which were administered at different times before or after the attempted intradermal sensitization had the same preventive effect as the injection in my first experiment. Biberstein and Oschinsky [56] found that they could sensitize a much smaller percentage of persons to guinea-pig serum when the persons employed were syphilitic and undergoing treatment than when patients who had not been treated with arsphenamine were used. As it is now impossible to ascertain how many of the syphilitic patients were being treated with arsphenamine, one cannot definitely decide to what degree their different behavior may be a result of the syphilitic infection or a result of the arsphenamine as a nonspecific means of preventing skin sensitization. (This possibility may be of practical importance and must be further examined.)

An added difficulty in attempting to find the cause of this immunity to sensitization lies in the fact that knowledge is lacking as to how long the preventive powers of the injection of arsphenamine may last. Considering the possibility mentioned, it must further be borne in mind that the refractory behavior of syphilitic patients which has been reported by other investigators in regard to other types of hypersensitivity (tuberculin, trichophytin, etc.) could perhaps be traced to this last named cause, and it seems that the intravenous administration of arsphenamine may have a nonspecific preventive influence on the development of many different types of skin allergy, and even of skin diseases.

It seems sufficiently established, then, that the experimental skin sensitization in animals and certain forms of the hypersensitivity to arsphenamine in human beings are probably due to related allergic mechanisms, and that in both the arsphenamine dermatitis may be a result of this allergy; further that a relationship exists between the prevention of sensitivity obtained in this experiment and that observed in man. It therefore seems allowable to seek to apply the new facts

56. Biberstein and Oschinsky: footnote 35; Klin. Wchnschr. **26**:1160, 1924.

57. Kyrle, Josef: Histobiologie der menschlichen Haut- und ihrer Erkankungen, 1927, vol. 2, p. 19.

gleaned from these experiments to practical dealings with certain types of arsphenamine idiosyncrasy, with only the necessary precautions which always must be observed in the application of the results of animal experiments to analogous processes in man. It is proved experimentally that the deposit of the smallest quantities of arsphenamine in the skin can produce a hypersensitivity. One conclusion to be drawn from this is that intravenous injections of arsphenamine should be undertaken only by the expert, and that a faultless technic and equipment are essential. Another practical hint, is that chance paravenous injections of arsphenamine, or any deposit of arsphenamine in the cutaneous or subcutaneous tissues, should not be followed by a pause of days or weeks in the intravenous injections, as heretofore may sometimes have been the case. On the contrary, this contretemps should be regarded as an indication that at least the full amount of the intended injection should be given (intravenously, of course), even after some of the fluid has been deposited outside the vein. One should also seriously consider, whether in view of the experimentally achieved prevention of sensitization, it might not be advisable to follow the paravenous injection by a second intravenous injection as soon afterward as possible. From my experiments on animals, it is, of course, impossible to say anything definite concerning the best doses for the second injection, nor after what interval of time it should be administered. It is further impossible to say whether this will prove an effective prophylaxis for arsphenamine dermatitis, as the dose given to guinea-pigs was from three to four times the equivalent of the usual maximum therapeutic dose for human beings. Experiments are now being conducted which will decide the question of whether one-third or one-fourth of the amount administered in the experiment reported will still prove effective in guinea-pigs. This last named amount represents about the quantitative equivalent of the dose for human beings on the basis of the ratio of the weights of guinea-pig and man.

It would also be interesting to ascertain whether the equivalent of the sensitizing human doses (which would be about one three-hundredth of the sensitizing dose heretofore employed) would sensitize the animals, and whether this small dose would not sensitize only a small number and so bring out even more clearly the idiosyncratic factor. This factor is already suggested in the different degrees of sensitiveness which were evidenced by the dermatitides of varying strength observed in experiment 2. (Such a result would coincide with the idiosyncratic sensitizations in human beings reported by Frei and by Nathan and Munk.)

While fully aware of the dangers and difficulties of generalization, it must be admitted that there may be a close relationship between the particular form of arsphenamine dermatitis studied and eczemas and occupational dermatitis. The similarities of their pathogenetic

mechanisms have been stressed by J. Jadassohn and Bloch, among others, and the resemblances between their histologic pictures, for instance, by Kyrle.[57]

It must nevertheless be left to the future to decide whether further experiments of the type here described will only further the study, prophylaxis and treatment of arsphenamine dermatitis, or whether they will prove of more general value. It seems to me not impossible that by this path new knowledge may be gained concerning the general processes of sensitizations, prevention of sensitizations and perhaps even of desensitizations of the skin, and that this may be of assistance in rationalizing and systematizing the use of these mechanisms in the prophylaxis and treatment of allergic skin diseases in general.

CONCLUSIONS

The skin of guinea-pigs can be sensitized to neoarsphenamine by intradermal injections of neoarsphenamine. Among other signs of this hypersensitiveness, the animals develop dermatitis on subsequent intracardial injection and hematogenous distribution of the drug. The hypersensitiveness of the animals and their dermatitides resemble the hypersensitiveness and certain forms of arsphenamine dermatitis observed in human beings. In guinea-pigs, the occurrence of this hypersensitiveness can be prevented by an introduction of the allergen (arsphenamine) into the blood stream, if this occurs soon enough (twenty-four hours) after the potentially sensitizing injection. When this same measure is applied after the hypersensitiveness has developed to a certain point (after fourteen days), no desensitization can be achieved.

This new fact concerning the prevention of sensitization suggests a possible way for the prophylaxis of arsphenamine dermatitis in human beings. Further study along these lines may enable one to find new rational immunologic measures for treatment and prophylaxis of other allergic skin diseases.

TOXIC REACTIONS PRODUCED BY THE APPLICATION OF TRINITROPHENOL (PICRIC ACID) *

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Trinitrophenol (picric acid) not only occupies a prominent place in the surgical field, but in its many combinations is utilized extensively in the treatment of diseases of the skin. When applied to the skin it may act in two distinct ways, according to the physical make-up of the subject.

(*a*) In one class, nonsensitive to this chemical, enough may be absorbed to produce severe visceral symptoms and even death. This is especially true when the surface of the skin has been abraded. The reaction from this type is due to the absorption of toxic amounts.

(*b*) Small amounts, which may be considered nontoxic when applied to the normal or abraded skin, will produce certain cutaneous, visceral and central nervous system reactions in the so-called sensitive person. It is in this class that we are particularly interested.

Owing to the wide distribution of ointment bases containing trinitrophenol, the general practitioner and even some specialists are using these preparations not only in the treatment of burns, but as an application for certain conditions about the eyes and the mucous orifices and especially for hemorrhoids and their complications. It is also highly recommended for certain diseases of the skin.

The percentage of persons sensitive to trinitrophenol is approximately 4.

Skin sensitization tests were made on 100 students. On one arm, an area 2 cm. square was painted with a 5 per cent alcoholic solution of trinitrophenol; on the other arm, a similar area was painted with 5 per cent aqueous solution of tannic acid. There were no reactions to the tannic acid, but 4 per cent of the patients showed positive reactions to the trinitrophenol, two reactions being severe and extending far beyond the area of application.

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* Submitted for publication, March 27, 1929.

* Read at the Fifty-Second Annual Meeting of the American Dermatological Association, San Francisco and Del Monte, Calif., July, 1929.

* Tests for trinitrophenol were made according to Peterson, Haines and Webster: Legal Medicine and Toxicology, Philadelphia, W. B. Saunders Company, 1923, vol. 1, p. 707; vol. 2, p. 720.

We have noted that in severe trinitrophenol dermatitis following the application of comparatively small amounts of this substance in sensitive persons, the typical eruptions showing the characteristic yellow tinge will also appear in areas to which the acid has not been applied. We concluded that this dermatitis occurring at a distance was produced by a protein picrinate which was carried by the blood stream or the lymphatics to these areas, where it was split up into its component parts and the trinitrophenol radical or some of its modifications reunited with the epithelial cells. In order to lend evidence to this belief, the following experiments were performed.

EXPERIMENTAL WORK

The skin of a dog that had just died was shaved and painted with a 5 per cent alcoholic solution of trinitrophenol, removed, dried, washed with alcohol to remove the free acid, and then redried. It was cut into small slices with a microtome, since it was impossible to pulverize it by any other method, then washed with saline solution until the results of all tests for trinitrophenol were negative in the washings. One gram of this pulverized skin was placed in a colloidal bag filled with saline solution and placed in a dialyzing chamber—the dialysate was tested for trinitrophenol with negative results. It was shown that a saline solution of trinitrophenol readily passed through this bag. This is evidence of the firm union of the trinitrophenol with the cells of the skin.

A gram of skin prepared as described was then washed with saline solution until the filtrate gave negative reactions for trinitrophenol. The residue was dried, washed with alcohol to make it sterile, redried and mixed with sterile saline solution and injected subcutaneously into dogs. Substances that gave reactions for trinitrophenol were present in the urine on the sixth and seventh days. The blood gave negative reactions. These results gave evidence that the protiopicrinate was split up by the dogs' metabolic processes.

This test for sensitization to trinitrophenol will be of great value to the surgeon. An area of skin 2 cm. square can be painted with trinitrophenol twenty-four hours before an operation is performed. If the patient is sensitive to this chemical, a marked dermatitis will make its appearance within twenty-four hours, giving the operator the opportunity to prevent a severe reaction and the patient the benefit of a more satisfactory convalescence.

REACTIONS

Local.—In our clinical observations we see many cases of dermatitis of the face, hands and feet and of the anal and scrotal regions, due to the local application of ointments containing trinitrophenol. The subjective and objective symptoms are severe, there being no mild types. The majority of these manifestations remain local, but some of them become severely systemic.

Intense itching and burning, accompanied by irritability, are common to nearly all. At some portion of the involvement, the color of the skin leads one to suspect trinitrophenol. Permanent yellow staining of the nails

of the hands and feet is diagnostic. The eruption itself is characterized by irregularly shaped macules, papules, vesicles, blebs, excoriations and edema, and by dried yellow crusts which are the source of reabsorption.

In the maculopapular stage, the purplish yellow is characteristic, even in the distant lesions. The disappearance of the eruption is the same as any acute dermatitis.

Generalized.—These localized reactions may not be considered allergic, but may be followed by generalized cutaneous reactions and constitutional symptoms which are allergic in their nature. In one case, constitutional symptoms of an alarming nature developed.

REPORT OF CASE

A man, aged 35, was superficially burned on his face and hands in a dust explosion. An ointment containing trinitrophenol was applied. In twenty-four hours, vesicles appeared accompanied by severe burning and itching. After each application of this preparation, the symptoms increased until the patient was almost frantic. He became so ill that it was necessary to send him to the hospital. When seen by us he had a generalized exfoliating dermatitis with universal edema. With the exception of the yellowish tinge to the skin the condition resembled that in acute arsphenamine dermatitis. After six weeks he had apparently recovered and was able to resume his work. In a few days he returned to us complaining of difficulty in walking. His speech, which had formerly been rapid and concise, was slow and scanning. In fact, he could not pronounce many words and was unable to repeat short sentences. The pupils were dilated and unequal and reacted poorly to light and in accommodation. A well marked spasticity of the right leg was present, the knee jerk was exaggerated with slight clonus, and the patient was unable to stand with his eyes closed. His gait ended in a mincing step. The blood pressure was systolic 190 and diastolic 120. The Wassermann tests of the blood and spinal fluid were negative. The spinal fluid also gave negative reactions to other standard tests. The blood chemistry was well within normal limits. No albumin, casts or red blood cells were found in the urine. The patient was again hospitalized and put on a milk diet. In three weeks all symptoms referable to the central nervous system disappeared, and the blood pressure was reduced to 130 systolic and 80 diastolic and has remained within normal limits since that time.

We consider that the involvement of the central nervous system in this case was due to the absorption of trinitrophenol.

Malmejac [1] has shown that trinitrophenol is found in the blood serum and even in the spinal fluid in persons who have suffered from the toxic effect of this chemical.

While trinitrophenol was not demonstrated in the spinal fluid of this patient, we could not account for the strange manifestations on any other basis. In two other cases we observed a severe generalized trinitrophenol exfoliating dermatitis due to an abdominal application of this substance. Nervous irritability seems to be a common observation in all severe cases of trinitrophenol dermatitis.

1. Malmejac: Toxicology, Paris letter, J. A. M. A. **68**:923 (March 24) 1917.

In the treatment of burns, trinitrophenol has a twofold purpose: (1) to precipitate the scorched proteins, converting them into a supposedly nonsoluble protiopicrinate or some of its derivatives (we have proved in our animal experiments that these precipitates are absorbed and produce toxic symptoms), and (2) to destroy bacteria by a coagulable process, which it probably does.

We strongly advise the discontinuance of the use of trinitrophenol in the treatment of burns and various dermatoses. We also warn surgeons against its use as a sterlizing agent preceding operations, due to the fact that many persons are sensitive to this chemical and because it is easily absorbed by the intact skin and taken up by the lymphatics and blood stream.

EXPERIMENTS TO DETERMINE THE LETHAL DOSE OF TRINITROPHENOL FOR DOGS WHEN SUBCUTANEOUS INJECTIONS OF THIS SUBSTANCE DISSOLVED IN SALINE SOLUTION ARE GIVEN

Dog 10 was given injections with 0.05 Gm. trinitrophenol in saline solution per kilogram of body weight. The animal became ill within twenty-four hours. In three days the skin was stained a yellowish brown. The blood chemistry was not noticeably influenced by this injection. Albumin, casts and red blood cells appeared in the urine on the seventh day, but disappeared on the sixteenth day. The dog recovered. Tests for trinitrophenol in the blood and urine by potassium cyanide and barium chloride were positive six days after the injection.

Dog 11 was given injections with 0.075 Gm. in solution per kilogram of body weight. The animal became ill on the third day. The blood chemistry was not noticeably influenced. Albumin, casts and red blood cells were found. Both tests for trinitrophenol were positive in the blood urine on this day, but were negative on the twelfth day. The dog recovered.

The same experiment was repeated on dogs 12 and 13, with practically the same results.

Dog 7 was given injections with 0.10 Gm. per kilogram of weight by the foregoing method. The catheterized urine twenty hours later was filled with albumin, casts and red blood cells. The blood was positive for trinitrophenol by potassium cyanide tests. The blood chemistry was normal. The animal recovered.

The same dog was given injections four days later with 0.125 Gm. in solution per kilogram of body weight. Two hours later, the animal had a convulsion, became unconscious—head thrown back, eyes bulging and incessant movement of legs—and died three hours later.

It appears that the lethal dose injected subcutaneously into dogs is between 0.1 and 0.125 Gm. per kilogram of body weight, since larger doses than the latter will kill the animal promptly.

Autopsy on these animals shows that the subcutaneous fat, even at points removed from the area of injection, is stained yellow. The lungs are often stained a brownish yellow. The liver sometimes shows a cloudy swelling, but is not stained. The kidneys show a glomerulitis, and also involvement of the substance, ranging from cloudy swelling to gelatinous degeneration. The intestines are stained yellow. The intima of the great vessels is often stained yellow. (The animals die from respiratory paralysis.)

1. It is shown from these experiments that as the lethal dose of trinitrophenol is approached, the positive reactions for this substance in the blood and urine appear with greater promptness, being positive in one and one-half hours after a lethal dose.

2. The sublethal doses down to 0.05 Gm. will show transitory changes in the kidney; these changes will disappear in a short time.

3. It was demonstrated that the trinitrophenol in the blood stream appeared as a protein combination, since the blood positive for trinitrophenol when passed through a colloidal bag gives a negative reaction to the cyanide method. It was also noted that an aqueous solution of trinitrophenol readily passes through a colloidal bag.

4. Chemical changes in the blood of dogs poisoned with trinitrophenol are slight. The urine of these same dogs nearly always shows albumin casts and red blood cells.

EXPERIMENTS TO SHOW THE AMOUNT OF ABSORPTION OF TRINITROPHENOL WHEN APPLIED TO THE NORMAL SKIN OF DOGS

The dog's skin does not have nearly the same ratio of absorption as the skin of a human being, since it has no sweat glands. Fifty cubic centimeters of a 5 per cent alcoholic solution of trinitrophenol was applied to the intact skin of the dog. The blood showed a positive reaction for trinitrophenol after twenty-four hours.

Tests for trinitrophenol in the blood of human beings who have received applications of trinitrophenol on the skin have not been done, but we are sure that these tests would be positive.

We have proved that a certain percentage of persons are sensitive to the external application of trinitrophenol to the intact skin. We believe that this phenomenon is a true allergic reaction, that the trinitrophenol radical can be broken off from the protein complement and redeposited as a protein picrinate in a new cell, and that this process can be repeated again and again. This repeated absorption can produce changes in other organs, especially of the central nervous system, producing bizarre manifestations which can be mistaken for other conditions of the brain.

We believe that in nonsensitive subjects trinitrophenol applied to the intact skin for surgical sterilization will be absorbed to such an extent that it can be detected in the urine and blood.

The application of a solution of trinitrophenol to burned or abraded skin is dangerous even for nonsensitive persons, since many deaths have been reported from its application.

CONCLUSIONS

1. Trinitrophenol used externally in any form is likely to be followed by disagreeable or dangerous results in a certain percentage of subjects.

2. The percentage of so-called sensitive persons is approximately 4.

3. In experimental work it was shown that in either subcutaneous injection or the external application of trinitrophenol, this substance would appear in the blood and urine of dogs, and while this observation has not been demonstrated in human beings because of the shortness of time in the work, we believe that the same results can be duplicated.

4. We advise against the use of trinitrophenol to sterilize the field of operation and recommend the substitution of tannic acid in proprietary ointment bases.

ABSTRACT OF DISCUSSION

Dr. William Allen Pusey, Chicago: I merely wish to say that I have seen cases of irritant dermatitis from butesin picrate.

Dr. Harry E. Alderson, San Francisco: I have seen a number of cases of dermatitis in patients whose skin was sterilized by solution of trinitrophenol (picric acid), and the dermatitis has extended far beyond the area to which it was applied. In a number of hospitals that I visit regularly this method of sterilization is used exclusively. I was talking to one of our leading surgeons, Dr. John Sperry, last week, and he has had a lot of experience with trinitrophenol. He said that in 255 cases in which he had performed an operation he had had no dermatitis, but in 4 per cent of the women who used a proprietary preparation containing picratol in the vagina an irritation developed extending over the outer surface. I spent two years as resident physician in a railway hospital twenty-five years ago, and it was common practice to cover the burns with a saturated solution of trinitrophenol. At that time no toxic effects were discovered.

Dr. Werner Jadassohn, Zurich: The great interest in the report of these authors lies, in my opinion, in the fact that 4 per cent of all persons whom they examined were hypersensitive to trinitrophenol. In contradistinction to its use in the United States, we employe this substance very little.

A percentage of 4 is high for hypersensitive subjects. We must, however, take into consideration that a strong concentration was employed. It is nevertheless certain that 4 per cent represents a minimum of those hypersensitive to this concentration. Dr. Staehelin of the Zurich Clinic is now investigating the effect of different methods of testing for eczematous reactions. In my opinion, the reactions observed by the authors are probably of this type. Staehelin's investigations have shown that through simple painting, as has been done in these investigations with trinitrophenol, positive reactions are noted much more rarely than if the test employed is our usual method of functional skin test for eczema. This consists in the laying on of a piece of soaked linen and covering it with oiled silk

and adhesive plaster. These tests are left in place twenty-four hours. A further reason that 4 per cent is probably a minimum is that according to our experience with other substances, reactions are sometimes observed only after more than twenty-four hours have elapsed. We have, therefore, made it a rule to examine the test site during several days. A third reason that 4 per cent represents a minimum number of persons really hypersensitive is that until now the authors have tested only for eczematous reactions. The testing for urticarial hypersensitiveness, through application of the substance to a scratch, would perhaps have revealed more hypersensitive persons through the appearance of a urticarial immediate reaction at the place of testing. In this manner, Stauffer in Zurich in testing with ipecacuanha found, besides the patients with eczematous reactions, a large number who reacted only urticarially. With certain other substances we can find only urticarial reactions as, for instance, with ascaris; or only eczematous reactions as, for instance, with primrose.

I mention these matters because it seems to me that the demonstration of the frequent hypersensitiveness to trinitrophenol is not only of importance practically, but also of interest theoretically, and could perhaps, through further work in various directions, be important in the research of eczema.

Dr. Arthur J. Markley, Denver: In reference to butesin picrate I think this is one of the most virulent local remedies on the market. It should be borne in mind that butyn itself is capable of producing a violent skin reaction and probably combining it with trinitrophenol makes it even more effective.

Dr. James Herbert Mitchell, Chicago: I wish to record an experience similar to that of Dr. Pusey's. Last year while I was attending the meeting of this association, an old man whom I was treating ran out of ointment and used butesin picrate. When I returned he was covered with a dermatitis and was ill. I am glad Drs. McBride and Dennie have called attention to the danger of applications of trinitrophenol.

Dr. Charles C. Dennie, Kansas City, Mo.: In the majority of our cases the dermatitis was due to the application of butesin picrate and in a smaller number it was due to the use of trinitrophenol alone. The eruption caused by the use of either is indistinguishable from the other. The percentage of sensitive persons is greater following the use of butesin picrate because some persons will be sensitive to both chemicals and some to either one. Our main attempt in this work was to show that the application of trinitrophenol or its compounds to the intact skin was followed by the absorbtion of the trinitrophenol into the blood stream and its deposition into the fixed tissues before it was excreted in the urine; and the redeposition theory which consisted of the union of the trinitrophenol with the fixed cells, its splitting off and transportation by the lymphatics or blood stream to a distant place where it united with a totally different cell, producing a manifestation which resembled the former condition.

We found that 0.125 of trinitrophenol per kilogram of body weight when injected subcutaneously in dogs would produce death. There was practically no change in the blood chemistry, although the urine would contain red blood casts and albumin and the tests for trinitrophenol were positive. In some instances the lining of the blood vessels was stained yellow and the liver showed some pathologic changes. The dogs died of respiratory failure. These observations proved the first contention.

The redeposition of trinitrophenol in cells at a distance from those originally affected was proved by the colloidal bag experiment, and the injection of the picric proteinate under the skin of dogs and the recovery of this substance in the blood and urine of these animals.

SUGAR METABOLISM IN ACNE VULGARIS*

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The probable relationship between metabolic errors and certain cutaneous diseases has received the increasing attention of dermatologists within recent years. As a result, numerous studies dealing principally with sugar metabolism and uric acid in such dermatoses as acne vulgaris, seborrheic dermatitis, eczema and furunculosis have made their appearance in dermatologic literature.

This paper is concerned with the study of the sugar metabolism in acne vulgaris. Acne vulgaris has been studied from this angle by such observers as Schwartz, Highman and Malinkin,[1] Levin and Kahn.[2] Schwartz and his associates reported hyperglycemia in acne vulgaris, and the studies of Levin and Kahn showed a high blood sugar in over 50 per cent of their thirty-eight patients with this condition.

This study of the sugar metabolism in acne vulgaris was undertaken in the hope of determining whether or not hyperglycemia is limited to a particular type of acne; whether the increase in sugar in the blood when present remains constantly at about the same level throughout the course of the disease; what influence, if any, limitation of sugary and starchy foods plays in increasing or decreasing the amount of blood sugar; whether the amount of blood sugar varies with clinical improvement or relapse; and to reaffirm the studies of others as to the percentage of cases of acne vulgaris showing hyperglycemia.

PLAN OF INVESTIGATION

With this objective in mind, whenever feasible, a number of determinations of the blood sugar were made in each case of acne vulgaris studied. This series consisted of thirty-nine patients.

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* Submitted for publication, May 13, 1929.

* From the Dermatologic Clinic of the Samaritan Hospital and from the Department of Physiologic Chemistry of the Temple University Medical School.

1. Schwartz, H. J.; Highman, and Malinkin: J. Cutan. Dis. **34**:159, 1916.
2. Levin, D. L., and Kahn, M.: Am. J. M. Sc. **164**:379, 1922.

The tables record the number of determinations made in each case of acne, the predominating type of lesion, the approximate duration of the ailment, the influence of limitation of sugary and starchy foods on the blood sugar and the relation between improvement or relapse and the blood sugar curve.

The preparation of the protein-free blood filtrate and the determination of dextrose was made by the Folin and Wu method. All the determinations were made by one of us (M. A. S.).

RESULTS OF EXPERIMENTS

Table 1 consists of the records of sixteen patients with acne vulgaris on whom only one determination of the blood sugar was made.

TABLE 1.—*Determination of Blood Sugar in Sixteen Cases of Acne Vulgaris*

Sex	Diagnosis	Duration	Predominating Type of Lesion	Determination of Sugar
F	Acne vulgaris	4 years	Papules and comedones	0.118
M	Acne vulgaris	2 years	Papulopustules	0.118
F	Acne vulgaris	15 years	Deep abscessed lesions, much scarring	0.099
M	Acne vulgaris	1 year	Papules, some scarring	0.089
F	Acne vulgaris	6 months	Papulopustules	0.122
F	Acne vulgaris	5 to 6 months	Pustules	0.118
F	Acne vulgaris	6 years		0.085
F	Acne vulgaris	2 years	Deep abscessed lesions	0.101
M	Acne vulgaris	1½ years	Deep papulopustules	0.095
F	Acne vulgaris	3 years	Papulopustules	0.079
M	Acne vulgaris	Uncertain	Deep abscessed lesions	0.102
F	Acne vulgaris	8 months	Papules and comedones	0.140
F	Acne vulgaris	1½ years	Papulopustules	0.070
M	Acne vulgaris	2 years	Papules and papulopustules	0.073
F	Acne vulgaris	3 years	Deep abscessed lesions	0.088
M	Acne vulgaris	2 years	Papulopustules and comedones	0.070

Analysis of table 1 shows that ten patients, or 62.5 per cent, had a blood sugar curve within normal limits; two, or 12.5 per cent, showed hyperglycemia, 122 and 140 mg., respectively, per hundred cubic centimeters of blood; and four, or 25 per cent, hypoglycemia, 70, 70, 73 and 79 mg., respectively, per hundred cubic centimeters of blood. The hyperglycemia and the hypoglycemia occurred in identical types of acne vulgaris, so that as far as this group is concerned, no definite relationship could be established between any abnormality in the percentage of blood sugar and a particular type of acne.

Table 2 records the determinations of blood sugar in seven patients with acne vulgaris. Here two examinations of the blood sugar were made, the first before the restricted diet was instituted and the second after the patients were placed on the diet. This consisted in the avoidance of candy, cake, ice cream and pie, and the limitation of sugar, white bread, potatoes, peas and beans.

A résumé of table 2 shows that in this series of seven patients the blood sugar previous to the institution of dietary restrictions was normal in five patients, or 70 per cent, while two, or 30 per cent, showed a hypoglycemia. After the dietary restrictions were followed for one or two months, the blood sugar was found to be increased in five instances, or 70 per cent, and to be slightly reduced in two. In this series no definite relationship could be established between the increase in the blood sugar and any particular type of acne, nor did clinical improvement coincide with any definite change in the amount of blood sugar.

Table 3 records the observations on a series of nine patients with acne on whom three determinations of blood sugar were made. Here

TABLE 2.—*Determination of Blood Sugar Before and After Restricted Diet in Seven Cases of Acne Vulgaris*

Sex	Diagnosis	Duration	Predominating Type of Lesion	First Determination	Second Determination and Time Interval	Clinical Result
F	Acne vulgaris	3 years	Comedones and papules	0.083	After 1 month, 0.081	Improved
F	Acne vulgaris	Several years	Papules and comedones	0.070	After 2 months, 0.118	
F	Acne vulgaris	3 to 4 years	Papulopustules and comedones	0.082	After 2 months, 0.115	Improved
M	Acne vulgaris	1 year	Comedones and papules	0.070	After 2 months, 0.121	
F	Acne vulgaris	2 or 3 years	Deep pustules and scars	0.088	After 2 months, 0.138	
M	Acne vulgaris	2 years	Comedones and pustules	0.080	After 2 months, 0.076	Much improved
F	Acne vulgaris	10 years	Comedones, papules and pustules	0.091	After 2 months, 0.120	Improvement

also, after the initial examination of the blood sugar, dietary regulations similar to those prescribed for the patients in table 2 were followed.

An analysis of the results of the first examination of the blood sugar shown in table 3 discloses observations similar to those in table 2. In this series of nine patients, seven gave normal results and two a hypoglycemia previous to the institution of dietary regulations. After a month of this restricted diet, the blood sugar was seen to rise in all but two instances, the greatest increase being from 74 to 99 mg. per hundred cubic centimeters of blood, while the smallest increase was from 87 to 89 mg. per hundred cubic centimeters of blood.

After two months or more of restricted diet, another determination of the blood sugar was made with the following results. In four instances examination of the blood showed results higher than those of the previous test, and in five instances the results were lower. The

latter determinations of the blood sugar, however, were higher in six instances and lower in three instances than the determinations made previous to the institution of the restricted diet.

The two principal types of determinations of the blood sugar here found are illustrated in chart 1.

TABLE 3.—*Results of Three Determinations of Blood Sugar in Nine Cases of Acne Vulgaris*

Sex	Diagnosis	Duration	Predominating Type of Lesion	First Determination	Subsequent Determinations and Time Intervals	Clinical Result
F	Acne vulgaris	5 years	Deep pustules and scars	0.083	After 1 month, 0.078 After 2 months, 0.075	No improvement Well and almost free of lesions
M	Acne vulgaris	2 years	.....	0.084	After 2 months, 0.107 After 3 months, 0.109	Improved Improved
F	Acne vulgaris	Indefinite	Sebaceous lesions, comedones, papulopustules	0.096	After 1 month, 0.114 After 3 months, 0.103	Improved Improved
F	Acne vulgaris	2 years	Deep papules, comedones	0.071	After 2 months, 0.081 After 3 months, 0.077	Improved
F	Acne vulgaris	Indefinite	Comedones, papules, scars	0.074	After 1 month, 0.099 After 2 months, 0.118	Improved Improved
F	Acne vulgaris	4 years	Papules and comedones	0.087	After 1 month, 0.089 After 2 months, 0.095	
F	Acne vulgaris	2 years	.....	0.098	After 2 months, 0.119 After 5 months, 0.095	Improved
F	Acne vulgaris	3 years	Deep papules and pustules	0.101	After 1 month, 0.098 After 2 months, 0.129	Improved
M	Acne vulgaris	1 year	Comedones, papulopustules	0.090	After 1 month, 0.114 After 3 months, 0.089	Improving

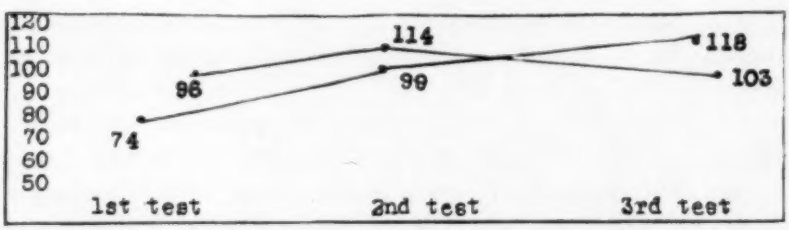

Chart 1.—Two types of determinations of the blood sugar.

Table 4 records the results of the studies on the blood sugar in seven patients with acne on whom four such determinations were made. As in the other series, the first determination of blood sugar was made before the institution of the restricted carbohydrate diet. The three other determinations followed at intervals of from one to two months.

A résumé of table 4 discloses the first blood sugar picture as normal in every case except one in which hypoglycemia was shown. A second examination made after the patients had been on a diet low in carbohydrate for approximately one month discloses an increase in the blood sugar in all but three instances. One of these three showed no

TABLE 4.—*Results of Four Determinations of Blood Sugar in Seven Patients with Acne Vulgaris*

Sex	Diagnosis	Duration	Predominating Type of Lesion	First Determination	Subsequent Determinations and Time Intervals	Clinical Result
F	Acne vulgaris	21 years	Deep papulo-pustules and scarring	0.087	After 1 month, 0.107 After 6 weeks, 0.097 After 10 weeks, 0.104	Slightly improved Same as above
M	Acne vulgaris of back; rosacea of face	1½ years	.....	0.090	After 1 month, 0.092 After 6 weeks. 0.152 After 2 months, 0.112	Improved Stationary
F	Acne vulgaris	15 years	Papules and comedones; scars	0.102	After 6 weeks, 0.093 After 3 months, 0.105 After 5 months, 0.114	 New outbreak
F	Acne vulgaris	1½ years	Deep pustules and scarring	0.085	After 1 month, 0.103 After 2 months, 0.118 After 4 months, 0.118	 Improved Improved
F	Acne vulgaris	8 years	Scarring	0.115	After 1 month, 0.113 After 2 months, 0.127 After 3 months, 0.101	Scarring, but acne almost gone Practically well Well
M	Acne vulgaris	4 years	Scars, lesions were deep papules	0.072	After 2 months, 0.101 After 4 months, 0.104 After 5 months, 0.129	Improved Improved Improved
M	Acne vulgaris	Indefinite	Papulo-pustules	0.099	After 1 month, 0.099 After 2 months, 0.084 After 3 months, 0.112	Improved Well

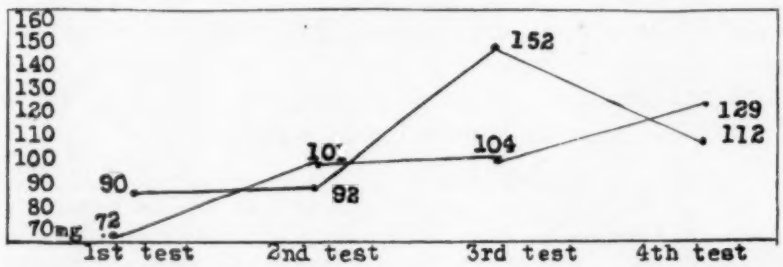

Chart 2.—Two types of blood sugar curves are shown: one in which the peak of the sugar concentration is reached rather early and then follows a decline; and another in which the blood sugar concentration keeps on climbing upward gradually without decline.

variation from the previous test, and the other two showed a decrease. After approximately two months of diet low in carbohydrates, a third determination of the blood sugar was made, and this showed a decrease in two instances and an increase in five. The fourth examination of the blood showed four increases from those in the third, two decreases

and one on a par. Here also the last determination of the blood sugar was higher in all but one instance than in the first test done before the institution of a diet low in carbohydrates.

It is apparent that the blood sugar in acne vulgaris undergoes cyclic variations with varying concentrations in the blood, as is exemplified in chart 2. A survey of the results discloses two types of blood sugar curves, one in which the peak of the sugar concentration is reached rather early and then follows a decline; and another in which the blood sugar concentration keeps on climbing upward gradually without decline. No doubt these facts explain the varying results obtained in acne by different observers when only one determination on the blood sugar is made.

There is, however, a more important phase of this problem which deserves attention. It concerns the possible alteration in the concentration of sugar in the blood and in the skin during certain stages of acne vulgaris. Usher and Rabinowitch [3] and Talbert and Silvers [4] showed that the normal of blood sugar in the sweat varies from 14 to 19 mg., but if dextrose is ingested by patients with both eczema and a diminished tolerance for sugar, the sugar excreted in the sweat rises to 34 or 40 mg. Usher and Rabinowitch also noted that while the normal amount of sweat varies from 67 to 115 cc. per hour, after ingestion of dextrose by those having eczema and a diminished tolerance for sugar, the amount of sweat secreted rises to about 335 cc. per hour.

In 1917, Palmer [5] reported on the concentration of sugar in the blood and skin of diabetic dogs, and his results disclosed that the amount of sugar in the skin was never more than 50 per cent of the amount of sugar in the blood.

Trimble, in his studies on the concentration of sugar in the skin of nondiabetic dogs, makes the following observations:

> In fasting dogs the concentration of sugar averages 65 mg. per hundred grams of skin when the blood sugar averages from 80 to 90 mg. per hundred cubic centimeters. When glucose is injected intravenously into dogs, the concentration also rises and reaches a numerical value only slightly lower per hundred grams of skin than that found per hundred cubic centimeters of blood. Samples of skin taken at various intervals after injections show that the sugar concentration of the skin and of the blood fall off in a nearly parallel manner. The concentration in the skin is always slightly under that in the blood.

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3. Usher, B., and Rabinowitch, I. M.: Excretion of Sugar in Sweat, Arch. Dermat. & Syph. **16**:706 (Dec.) 1927.

4. Talbert, G. A., and Silvers, S. H.: Personal communications to Dr. Greenwood.

5. Palmer, W. W.: J. Biol. Chem. **30**:79, 1917.

CONCLUSIONS

1. From our studies as well as from the facts elaborated by other observers, it would appear to us that in acne vulgaris a relationship may exist between the concentration of sugar in the blood and in the skin.

2. This altered concentration of sugar might explain the great number of pyogenic lesions seen in certain types of acne, for Usher has recently shown that sweat of human beings is an excellent culture medium for certain bacteria, and that the activity of the bacterial growth in sweat appears to vary directly with the sugar content.

3. In this series of thirty-nine patients, the first determination of the blood sugar showed twenty-eight normal results, two instances of hyperglycemia and nine instances of hypoglycemia. The highest concentration of blood sugar in the first determinations of the blood sugar was 140 mg.

4. In this study, eighty-five determinations of the blood sugar were made with the following results: sixty-four, or 75 per cent, showed normal observations on the blood sugar; thirteen, or 15 per cent, showed a hypoglycemia, and ten, or approximately 10 per cent, a hyperglycemia.

This study is submitted as a preliminary report, and a more extensive study is now under way.

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Abstracts from Current Literature

PEMPHIGUS PRIMARY IN THE LARYNX. ALBERT B. MURPHY, Arch. Otolaryng. **10**:188 (Aug.) 1929.

A case of pemphigus is reported in a man, aged 72, in whom the lesions were restricted to the larynx for a period of twelve weeks before there was involvement of the skin and mucous membranes elsewhere.

CONTROL OF IMPETIGO NEONATORUM. E. T. RULISON, J. A. M. A. **93**:903 (Sept. 21) 1929.

As a means of controlling epidemic neonatal infections, the author has adopted small nurseries with individual baby units which contain all necessities for the baby's care. A schedule was instituted whereby nurses were responsible for the care of only a limited number of patients. The plan, outlined in detail by the author, can be adopted at little added expense to the hospital, and has proved satisfactory.

TINEA OF THE TOE-NAILS AS A SOURCE OF REINFECTION IN TINEA OF THE FEET. CHARLES MALLORY WILLIAMS and ELSE A. BARTHEL, J. A. M. A. **93**:907 (Sept. 21) 1929.

In forty cases of tinea pedis, an organism of the ringworm group was recovered from the toe-nails, which were apparently normal. The abnormality of the nails was so slight that the patients were seldom aware of it; it consisted of slight discoloration, a dull rather than a shiny surface and a few longitudinal striae. The organisms were found in the nails long after the cutaneous symptoms had disappeared, and are probably the source of reinfection in many cases of tinea of the feet.

EPIDERMOLYSIS BULLOSA. JOSEPH GARLAND, J. A. M. A. **93**:918 (Sept. 21) 1929.

In the case reported, the lesions were present at birth. Delivery was normal without instrumentation.

ALOPECIA AREATA. RONALD B. ROGERS, J. A. M. A. **93**:919 (Sept. 21) 1929.

A man, aged 37, had had three attacks of alopecia areata of the scalp. Each attack followed the birth of a child, and on one occasion following the birth of a stillborn child, he had no attack. The case is offered as evidence of the psychic origin of alopecia areata, the attacks being due to worry over the added expense of raising a child, for after the birth of a stillborn child there was no alopecia.

EXFOLIATIVE DERMATITIS FROM POTASSIUM SULPHOCYANATE THERAPY. CLIFFORD WEIS and RUDOLPH RUEDEMANN, J. A. M. A. **93**:988 (Sept. 28) 1929.

The drug was used for essential hypertension. The dermatitis began on the tenth day of medication.

METALLIC MERCURY IN SUBCUTANEOUS TISSUE. CAPT. C. A. STAMMEL, Mil. Surgeon **65**:529 (Oct.) 1929.

Two months after a mercurial inunction, a roentgenogram showed a dense shadow due to metallic mercury in the subcutaneous tissue of the thumb and forearm. The patient had rubbed blue ointment on his thumb. Three weeks later there developed several fluctuant, bluish tumefactions which, when incised, revealed minute globules of mercury in the exuding serum. The patient showed no signs of mercurial poisoning.

THE DEPIGMENTED PATCH IN LEPROSY: A CLINICAL AND PATHOLOGICAL STUDY. JOHN M. HENDERSON, Indian J. M. Research **17**:33 (July) 1929.

The author describes several varieties of depigmented patches: The first, a perifollicular type, consists of a collection of discrete pinhead-like spots around the mouths of the hair follicles. In these there is also a mild degree of hyperkeratosis, giving the lesion a sensation of roughness. This is a lesion of recent occurrence. The second form is a uniformly depigmented area of varying size. The edge of the patch may shade off into apparently normal skin or may present a perifollicular zone of depigmentation. The latter indicates a progressive lesion when it occurs in a patch which has hitherto presented a uniformly depigmented appearance; it is indicative of a reactivation of the skin. These lesions are older than the perifollicular type. The third type consists of large plaque-like lesions with well marked keratosis — a chronic lesion. A fourth type, the zone type, represents a transition stage between the true depigmented patch and the erythematous lesion, and appears as a large depigmented patch bounded by a raised erythematous border. Finally, there is the mottled type in which there is a return of pigment around the mouths of the hair follicles — usually seen in patients who have been treated. In general, recent patches show more depigmentation than those of longer standing. Anesthesia to light touch is commonly present in the flat depigmented patch and in the plaque type of lesion; paresthesia is more common in the perifollicular lesions. In the zone type, there is anesthesia in the center and paresthesia in the periphery. The histologic appearances of the various types are described in detail and consist in the main of proliferation of endothelial-like cells in the papillae of the corium, and an increase in the numbers of mast cells. There is a diminution in the concentrations of melanin pigment granules. In the patches the organisms are few in number, and in those of long standing none may be found. The author attempts to correlate the clinical picture with the histologic observations. He considers the depigmented patch to be the initial lesion in a large number of cases of leprosy. The paper contains some excellent photographs and photomicrographs.

RATTNER, Chicago.

FORDYCE'S DISEASE. V. PARDO CASTELLO and JUAN JOSE MESTRE, Bol. Soc. Cubana de dermat. y sifil. **1**:3 (June) 1929.

A mulatto woman, aged 31, had Fordyce's disease involving the axillae, labia majora, mons, areolae of the breasts and inner side of the right thigh. The skin was lichenified. Sections showed inflammation and degeneration of the sweat glands with cystic enlargement of the lumen, follicular hyperkeratosis and acanthosis. Treatment with ovarian extract administered internally, and the roentgen rays applied locally apparently effected a cure.

AUTHORS' SUMMARY.

THE ETIOLOGY OF ALOPECIA AREATA. R. SABOURAUD, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:31 (March) 1929.

In this clinical lecture, Sabouraud discusses this question in detail. He rejects the idea of a microbic cause; neither the clinical features of the disease nor any laboratory investigations permit, at present, an infectious theory. The cause is endogenous.

The autochthonous causes are then discussed. An hereditary influence was noted in 22 per cent of the cases. Sabouraud has seen the disease in four generations of the same family. A syphilitic inheritance is important in children.

Among concomitant causes, the menopause is important, also exophthalmic goiter.

In regard to the pathogenicity of the disease, there seems to be an inhibition of the function of the hair papilla. This seems plausible, since in most cases there is a constant tendency to form hair, which, however, until normal growth appears is of the lanugo type. The underlying cause of this inhibition is obscure, but it probably resides in some malfunction of the sympathetic system.

CUTANEOUS MANIFESTATIONS ACCOMPANYING PRIMARY SPLENOMEGALY: THE CUTANEOUS ASPERGILLOSES. A. NANTA, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:50 (March) 1929.

Nanta discusses a syndrome which he has studied for several years. It consists essentially of splenomegaly and, in nearly all cases, an ulcer of the leg. The splenomegaly is due to an aspergillosis; the relation of the cutaneous ulcer to the splenic infection seems certain, but whether it acts as a portal of entry or is only a concomitant manifestation is an open question. It is significant that splenectomy in this disorder has been followed by healing of the ulcer of the leg.

The author has produced splenomegaly in the rabbit with *Aspergillus* obtained from affected human spleens. In the skin and viscera of the rabbit, altered forms of *Aspergillus* were found. In one instance, an amicrobic abscess of the skin appeared in a rabbit.

GOLD SALTS IN THE TREATMENT FOR CUTANEOUS TUBERCULOSIS. M. BURNIER, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:69 (March) 1929.

Burnier summarizes the present state of knowledge concerning these preparations. His personal experience has been practically confined to gold compounds and sodium thiosulphate. He gives this drug in courses of twenty weekly injections, when necessary, repeating the course after a month's rest. The dose is 10 mg., increased to a maximum of 25 mg. His best results and greatest experience have been in lupus erythematosus. He has found that the more superficial, erythematous types respond quickest; the fixed, infiltrated types more slowly than the preceding. In thirty-eight cases of lupus erythematosus, there were twenty-five cures, seven improvements and six failures. There were six recurrences of apparently cured cases; these responded to further treatment. In two of three cases of lupus vulgaris the patients were unresponsive; in one, the patient was cured. One patient with papulonecrotic tuberculids was cured with eight doses.

There were a few instances of intolerance to the drug, of mild types chiefly.

THE CUTANEOUS GLANDS. O. ELIASCHEFF, Arch dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:85 (March) 1929.

In this lecture to a group of postgraduate students, Eliascheff gives an excellent presentation of this subject. The article contains no new facts.

ÉRYTHÈME PAPULOSQUAMEUX CIRCINÉ LEUDODERMIQUE. H. GOUGEROT and P. BLUM, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:93 (March) 1929.

With this designation, the authors report a case presenting a clinical syndrome which seemingly has not been previously described.

The patient was a young woman, a native of Hungary. She presented a chronic eruption on the trunk and thighs, which was rebellious to treatment and slightly pruriginous. Neither the etiology nor the pathogenicity could be determined.

The lesions were numerous, scattered without order, beginning as a small, pink, slightly scaly papule. Confluence of the elementary lesion led to circinate patches, the center of which became achromic and superficially atrophic. The histology conformed to the clinical appearance without presenting special features.

PAPILLOMATOSE PAPULEUSE CONFLUENTE ET RETICULÉE. H. GOUGEROT and A. CARTEUD, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:102 (March) 1929.

Under this name, or under that of papillomatose papuleuse pigmentée et reticulée, the authors recorded their observations in three cases of what appears to be an undescribed dermatosis.

It is characterized by verrucous papules of from 2 to 4 mm., resembling verruca plana juvenilis, which soon become confluent into more or less extensive patches producing a reticulated pattern. The lesions begin and predominate in the inter-

mammary and epigastric regions, but may invade other areas of the trunk. In the axillae they form a diffuse papillary field with accentuation of the normal skin lines. The evolution is chronic and the etiology unknown. Carbon dioxide snow gave the best therapeutic results.

THE MILIARY RED PAPULE: ELEMENTARY LESION OF POIKILODERMA (PETGES-JACOBI). H. GOUGEROT and O. ELIASCHEFF, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:137 (March) 1929.

While a miliary papule has been described in poikiloderma, the authors do not believe that it has been accorded the importance it possesses; namely, that of the initial lesion of the disease. They describe this papule as rose or red, from 1 to 2 mm. in diameter, brilliant, lichenoid, sometimes capped with a fine scale and slightly infiltrated to palpation. Histologically, there is epidermal atrophy with marked edema and cellular collections in the papillary body.

Clinically and histologically, all transitions between this papule and the other residual lesions of poikiloderma can be found. Two cases of poikiloderma exemplifying the various changes from the initial papule to the end-stages are described.

TUBERCULOUS ROSEOLA: DISSEMINATED, ACUTE, LUPUS ERYTHEMATOSUS WITH ROSEOLAR ERUPTION: AUTOPSY. GOUGEROT, BARTHELEMY AND LOTTE, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:147 (March) 1929.

The authors describe a roseolar eruption in a patient with acute pulmonary tuberculosis. The cutaneous eruption was due probably to a tuberculous bacillemia. Syphilis was excluded. Kaposi described a roseolar eruption in disseminated lupus erythematosus, but it is rare.

A NEW CASE OF SCLERODERMIFORM TUBERCULOUS SARCOID (GOUGEROT-DENECHEAU). H. GOUGEROT and BURNIER, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:155 (March) 1929.

The authors discuss in detail a little known form of sarcoid, the sclerodermiform. This variety is divisible into three types: (1) chronic, with tuberculoid structure; (2) acute, and (3) chronic, affecting the extremities and trunk, of nontuberculoid structure (Gougerot and Denecheau). The latter is the most frequent. They describe two cases, one previously reported. Their present case showed both sclerodermiform and disseminated nodular sarcoids. There was a demonstrable visceral tuberculosis. A nodular sarcoid was produced by the injection of tuberculin. Tuberculin therapy caused disappearance of the lesions in six weeks.

LUPUS MILIARIUS DISSEMINATUS. GOUGEROT, BARTHELEMY and LOTTE, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:169 (March) 1929.

A case is reported in which typical lupomas, as well as lesions suggesting acnitis, were present. The case presented interesting differential diagnostic problems.

EPITHELIOMA OF THE NOSE ARISING ON EXTINCT LUPUS ERYTHEMATOSUS. BURNIER, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:174 (March) 1929.

Burnier records a case of spinocellular epithelioma appearing in the scar of lupus erythematosus. This sequela is rare; so far, the results in only sixty-seven similar cases have been published. In the present case, only scarification had been employed in the treatment for the lupus erythematosus.

NEVUS ANGIOMATOSUS WITH ATROPHIC ZONES, NOT PRECEDED BY ULCERATION. H. GOUGEROT and BURNIER, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:177 (March) 1929.

An infant, aged 6 months, presented an extensive port wine mark, which was undergoing regression without ulceration. The cleared zones, however, showed atrophy.

A Case of Melanosis of Riehl. M. Burnier and O. Eliascheff, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:182 (March) 1929.

The patient was a woman, aged 53. The disease was practically confined to the neck, appearing as brownish pigmentation in areolar pattern. There was a faint associated atrophy. In this case the etiologic hypothesis of Habermann that the disease is due to a photodynamic substance derived from tar distillate, thus a dermatosis industrialis, could be sustained with some probability.

Keloids Arising on Postzosteriform Scars. H. Gougerot, Carteud and Sidoun, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:186 (March) 1929.

In this case, zoster occurred in 1921, while the keloids appeared in 1927.

Lichen Planus Limited to the Scars of Zoster. H. Gougerot and Filliol, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:189 (March) 1929.

The patient presented lichen planus limited to the scars of zoster, the latter disease having preceded the former by several months. Lichen spinulosus was present in adjacent areas. The authors conjecture that the zoster cicatrices formed a point of lowered resistance for a latent lichen planus.

Delayed Development of Psoriasis on a Scar. H. Gougerot and P. Blum, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:193 (March) 1929.

The disease developed on an operative scar four years after an operation on the neck. Disseminated patches occurred simultaneously.

Psoriasis Precipitated by Sunlight. H. Gougerot, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:195 (March) 1929.

While the beneficial effect of light on psoriasis is well known, there are a few cases in which sunlight precipitates the disease. In some of these instances there is an enhanced sensitivity to light; in others, none. Exceptionally, both ultraviolet light and roentgen rays bring out new patches of the disease, and therefore, the author thinks it advisable to test the effect of these agents on a limited cutaneous area before instituting treatment with them.

Gonorrheal "Chancre." H. Gougerot, Burnier and P. Blum, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:201 (March) 1929.

The gonococcus may produce ulcerations simulating either chancre or chancroid. Many texts do not mention this possibility; hence, the authors have collected the literature on this subject and report a case of their own. The diagnosis must be confirmed by laboratory study.

Gonococcal "Chancre" Simulating True Chancre and Chancroid. H. Gougerot, A. Carteud and A. Tardieu, Arch. dermat.-syph. de l'hôp. St.-Louis (Paris) **1**:211 (March) 1929.

The reported case was interesting because there were penile lesions due to the gonococcus which resembled chancroid, syphilitic chancres and papular syphilids. The true nature of the lesions was determined by laboratory examinations.

Buccal Lichen Planus: Failure of Spinal Roentgen Therapy. Maire and Woringer, Bull. Soc. franç. de dermat. et syph. **36**:480, 1929.

A case is reported in which filtered roentgenotherapy to the cervical region was ineffectual. In the discussion, Pautrier remarked that failures were the rule with spinal radiation in buccal lichen planus.

SPASMODIC MYOPIA DUE TO NEOARSPHENAMINE. REDSLOB and G. LEVY, Bull. Soc. franç. de dermat. et syph. **36**:483, 1929.

A case of the development of this disturbance during a series of injections of neoarsphenamine for primary syphilis is recorded.

"BOUTON D'HUILE" IN AN AUTOMOBILE FACTORY-HAND. L. M. PAUTRIER and DISS, Bull. Soc. franç. de dermat. et syph. **36**:486, 1929.

The patient presented yellowish, thickened and roughened skin studded with firm, conical papules on the upper and lower extremities. These parts were constantly bathed in oil.

FOX-FORDYCE DISEASE IN A YOUNG MAN. L. M. PAUTRIER, Bull. Soc. franç. de dermat. et syph. **36**:489, 1929.

A youth, aged 17, presented typical lesions of this disease in the axillae and about the nipples.

TREATMENT OF TINEA CAPITIS BY THALLIUM ACETATE EPILATION. L. M. PAUTRIER and WORINGER, Bull. Soc. franç. de dermat. et syph. **36**:491, 1929.

Employing doses of 8 mg. per kilogram of body weight, the authors obtained eight cures in ten cases. The failures were apparently due to an early regrowth of the hair. No severe untoward effects were produced by the remedy.

THE POSSIBILITY OF OBTAINING A TYPE CULTURE OF A DERMATOPHYTE FROM AN APPARENTLY PLEOMORPHIC ONE. K. BEINTEMA, Bull. Soc. franç. de dermat. et syph. **36**:494, 1929.

The author had an old, apparently pleomorphic culture of a dermatophyte that he wished to examine in its original form, if possible. He found that it still retained a few fuseaux. His method of recovering the original culture consisted in taking up a small amount of the pleomorphic culture on a platinum loop and making a streak preparation on Sabouraud's medium. The platinum loop just broke the surface of the medium. Isolated primitive cultures developed and were transplanted.

PIGMENTED BASAL CELL EPITHELIOMA OF THE SCALP. L. M. PAUTRIER and DISS, Bull. Soc. franç. de dermat. et syph. **36**:498, 1929.

The authors report a case of cylindroma which microscopically contained a considerable amount of pigment. The pigment was found in macrophages and in Langerhan's cells. It was evidently produced by the latter, and possibly by basal cells, though its origin from the latter could not be demonstrated as the dopa reaction could not be done. The most plausible explanation of the presence of numerous Langerhan's cells is that there was an intertumoral multiplication of them.

EPITHELIOMA OF SUDARIPAROUS ORIGIN. HUFSCHMITT and DISS, Bull. Soc. franç. de dermat. et syph. **36**:503, 1929.

The authors report a case of a tumor of the scalp composed of cells of sweat gland origin.

DEVELOPMENT OF LICHEN PLANUS ON AREA EXPOSED TO SPINAL ROENTGENIZATION. J. NICOLAS and J. ROUSSET, Bull. Soc. franç. de dermat. et syph. **36**:506, 1929.

The patient had hyperkeratotic lichen planus of the legs for which he received spinal irradiation over the cervical and lumbar region. Soon after, these irradiated areas exhibited a profuse lichen planus eruption.

ACTIVE SYPHILIS RESISTANT TO TREATMENT. J. GATE, H. GARDERE, G. BOSONNET and P. MICHEL, Bull. Soc. franç. de dermat. et syph. **36**:509, 1929.

The authors presented a patient with tertiary syphilis in whom lesions of the disease developed despite specific therapy. On account of intolerance to arsphenamine, mercury and bismuth were employed. In addition to dermal manifestations, both renal and pulmonary lesions occurred.

THE TREATMENT OF BUCCAL HYDROA. J. GATE, G. BOSONNET and P. MICHEL, Bull. Soc. franç. de dermat. et syph. **36**:515, 1929.

A patient, aged 29, presented scattered erosions of the buccal mucosa. After two weeks of treatment with gargles, nitrate of silver and methylene blue applications, a cure was obtained.

SECONDARY SYPHILITIC SPLENITIS. J. GATE, G. BOXONNET and P. MICHEL, Bull. Soc. franç. de dermat. et syph. **36**:520, 1929.

A pregnant woman presented a chancre for which neoarsphenamine was given. Intolerance to this drug necessitated the substitution of mercury cyanide and bismuth. After delivery she developed pain in the left hypochondrium, splenomegaly and fever, which receded under treatment with bismuth.

A CASE OF DERMATITIS OF THE LEGS WITH FEATURES OF LICHEN OBTUSUS AND LICHEN CORNÉ. J. GATE, G. BOSONNET, P. MICHEL and A. VIDAL, Bull. Soc. franç. de dermat. et syph. **36**:525, 1929.

An aged patient, with edema of the legs, presented a dermatitis of these parts followed by lichenification. On this field lesions developed suggesting lichen obtusus and lichen corné. The case was presented to bring out a discussion of Pautrier's conception of lichen obtusus and lichen corné as atypical neurodermatitis. In the main, the discussers regarded the lesions in this case as a consequence of stasis.

FLAT EPITHELIOMA OF THE THIGH; CLINICALLY OF PAGETOID; ANATOMICALLY OF BASAL CELL TYPE. J. NICOLAS, G. MASSIA and J. ROUSSET, Bull. Soc. franç. de dermat. et syph. **36**:527, 1929.

The lesion was of the plane type, suggesting a pagetoid epithelioma, but microscopic study revealed a pure basal cell structure. The authors believe that Paget's disease occurs in extramammary locations.

ASSOCIATION OF TUBERCULOSIS VERRUCOSA CUTIS AND TUBERCULOUS OSTEOCHONDRITIS. J. NICOLAS, J. LACASSAGNE and J. ROUSSET, Bull. Soc. franç. de dermat. et syph. **36**:532, 1929.

The case was of interest because of the association of these two forms of tuberculosis.

UNTREATED ACTIVE SECONDARY SYPHILIS WITH NEGATIVE WASSERMANN REACTION. SPILLMAN and LAVERGNE, Bull. Soc. franç. de dermat. et syph. **36**:537, 1929.

The authors report a case of active secondary manifestations (condyloma lata) with repeatedly negative Wassermann reactions. There was definite response to syphilitic medication. The case is one of a number which have been reported in recent years in France. While it was formerly thought that the negativity in these cases was due to technical errors, it seems that this idea must be revised. Intensive study of such cases is in order.

PERSISTENT MERCURIAL TREATMENT OF SYPHILIS. SPILLMANN, Bull. Soc. franç. de dermat. et syph. **36**:541, 1929.

Spillmann's experience with syphilitic patients followed for many years and treated by Fournier's formula, leads him to believe that this is an effective treatment. While he respects the results obtained with more modern treatment, there is some question whether the older methods were not too hastily discarded.

TREATMENT OF VARICOSE ULCERS WITH VENOUS SCLEROSIS AND UNNA'S ZINC BANDAGE. E. M. JACQUET, Bull. Soc. franç. de dermat. et syph. **36**:544, 1929.

In twenty-eight cases, employing this combined treatment, excellent results were obtained. Sodium salicylate (10-30 per cent) solutions were used as the sclerosing agent. There are practically no contraindications to the method and no untoward effects.

ALKALOSIS IN DERMATOSES. SPILLMANN, DROUET and VERAIN, Bull. Soc. franç. de dermat. et syph. **36**:546, 1929.

The authors investigated several skin diseases for an associated alkalosis. They employed Van Slyke's method for the determination of the alkali reserve and the electrometric method for the acid-base equilibrium. Their results show that in a certain number of dermatoses (eczema in particular) alkalosis is present and that appropriate attention to it by means of diet and acid medication, gives favorable therapeutic response.

ECZEMA MARGINATUM IN A NURSLING. L. PERIN, Bull. Soc. franç. de dermat. et syph. **36**:580, 1929.

The eruption, typical of this disease, began during the third week of life. Scale preparations were positive for fungi.

EXPERIMENTAL INVESTIGATIONS ON IMPETIGO HERPETIFORMIS. G. MILIAN, Bull. Soc. franç. de dermat. et syph. **36**:580, 1929.

Cultures of the pustular contents, corneal inoculations in rabbits and injection of the blood of a patient into guinea-pigs failed to reveal a microbic cause of the disease.

IMPETIGO RODENS AND ENDOCARDITIS. G. MILIAN, NATIVELLE and CAROLI, Bull. Soc. franç. de dermat. et syph. **36**:582, 1929.

The patient presented a bullous and ulcerative skin disorder in which streptococci were found. He died of streptococcic endocarditis.

FACIAL PARALYSIS AND SYPHILITIC HYDRARTHROSIS. EFFECT OF OUABAIN ON A NITRITOID CRISIS. J. CAROLI, Bull. Soc. franç. de dermat. et syph. **36**:584, 1929.

In a patient with old syphilis, a severe nitritoid crisis was promptly relieved by the intravenous injection of 0.25 mg. of ouabain.

ATROPHIC PAPULOSQUAMOUS TUBERCULIDS AND LUPUS ERYTHEMATOSUS. H. GOUGEROT and P. BLUM, Bull. Soc. franç. de dermat. et syph. **36**:587, 1929.

Associated with a typical discoid lupus erythematosus were disseminated psoriasiform lesions with the histologic structure of lupus erythematosus.

INFECTIOUS ERYTHEMA OF THE NINTH DAY: ERYTHEMATOPURPURIC TYPE. P. BLUM, Bull. Soc. franç. de dermat. et syph. **36**:588, 1929.

A patient with early secondary syphilis, undergoing intensive treatment, developed a generalized erythematopurpuric eruption. There was a question of

arsphenamine intolerance, but this was dismissed because of the absence of pruritus, the character of the eruption and its accompanying systemic symptoms.

POSTARSPHENAMINE AGRANULOCYTOSIS WITHOUT ANGINA OR HEMORRHAGE. GOUGEROT, BARTHELEMY and P. UHRY, Bull. Soc. franç. de dermat. et syph. **36**:590, 1929.

Following an intensive course of arsphenamine, the patient presented marked anemia and leukopenia with agranulocytosis.

DISSEMINATED TUBERCULOSIS VERRUCOSA CUTIS FOLLOWING MEASLES. A. SEZARY and POUMAILLOUX, Bull. Soc. franç. de dermat. et syph. **36**:597, 1929.

A patient, aged 15, exhibited numerous lesions of verrucous tuberculosis, which had appeared in successive crops following uncomplicated measles. On the skin typical patches of lupus vulgaris were also present. The original focus of the infection could not be determined.

IS THERE A CONTAGIOUS ALOPECIA AREATA? L. BORY, Bull. Soc. franç. de dermat. et syph. **36**:599, 1929.

In a short philosophic communication, in which the evidence for and against this question is briefly summarized, Bory concludes that an absolute denial of an infectious pelade is not permissible. In some cases the disease may result from traumatism or infection of the sympathetic ganglions.

EXPERIMENTAL STUDY OF THE ETIOLOGY OF PSORIASIS BY MEANS OF VACCINE: PRELIMINARY REPORT. L. BORY, Bull. Soc. franç. de dermat. et syph. **36**:603, 1929.

Bory attempted to throw light on the etiology of psoriasis by noting the effects of an enterovaccine on the disease. His therapeutic results were not uniform, but he believes that his method of study may supply useful information.

BIOLOGIC AND IMMUNOLOGIC STUDIES ON YEASTS IN ONE HUNDRED AND THIRTY-SEVEN PATIENTS WITH VARIOUS DERMATOSES. P. RAVAUT, RABEAU, LONGHIN and SLOIMOVICI, Bull. Soc. franç. de dermat. et syph. **36**:607, 1929.

In a continuation of their studies on yeast infections of the skin, the authors present the results of bacteriologic and immunologic researches on a series of diverse skin diseases. Their studies are incomplete in the sense that they used but one yeast (*Cryptococcus*) for intradermic, complement-fixation and precipitation tests. They recovered yeasts by scale or culture methods in 13 of 150 patients with various suppurative or exudative lesions. They examined patients with epidermophytosis, tuberculids, lupus erythematosus, parapsoriasis, psoriasis, eczema and several other dermatoses for the presence of yeasts, cutaneous reaction to a yeast preparation and trichophytin, complement-fixation and precipitation reactions to yeast antigen.

They conclude that yeasts are not pure saprophytes. These organisms are capable of producing immunologic reactions. The coincidence of the presence of yeasts and of immune reactions in certain intertrigos and eczematids confirm the author's contention that those organisms cause the disease mentioned.

The absence of yeasts and negative immune reactions in some of the dermatoses studied (psoriasis, parapsoriasis, eczemas) show that it is improbable that yeasts cause these disorders.

DERMATOLOGIC OBSERVATIONS DURING THE EPIDEMIC OF 1928 IN ATHENS. N. DRACOULIDES, Bull. Soc. franç. de dermat. et syph. **36**:612, 1929.

The pyodermas were the most common and serious cutaneous complications noted.

A Case of Érythème Annulaire Centrifuge Pemphigoid. J. G. Uruena, Bull. Soc. franç. de dermat. et syph. **36**:615, 1929.

The disorder began as a typical example of this disorder; then exhibited bullae. During the bullous stage severe systemic symptoms appeared. Later, the disease resumed its usual aspect.

Macular Leprosy in Negroes. E. Marchoux, Bull. Soc. franç. de dermat. et syph. **36**:619, 1929.

Marchoux presented a negro with insignificant signs of the disease and called attention to the danger of the spread of the disease in France by reason of early cases among the colonial troops. Sometimes Hansen's bacillus can be demonstrated by gland puncture.

Michael, Houston, Texas.

DERMATOLOGIC ABSTRACTS

The Journal of the American Medical Association

Temporary Edema of Face Following Treatment of Exophthalmic Goiter. W. O. Thompson and P. K. Thompson, Am. J. M. Sc. **178**:73 (July) 1929.

Nine cases are presented by the Thompsons in which temporary edema of the face occurred following treatment for exophthalmic goiter. The nature of this edema is discussed.

Incidence of Etiologic Factors in Pruritus Ani. J. F. Montague, M. J. & Rec. **130**:63 (July 17) 1929.

A study made by Montague of the primary causes in 349 cases showed that certain commonly accepted causes, such as the presence of worms and the existence of diabetes, are not really common. In the majority of cases anorectal diseases were primary causes and in order of frequency these were coloproctitis, chronic anal fissure, undetected fistulas and hemorrhoids. Food allergy and the existence of pelvic visceral disease are definite overlooked factors in the causation of some cases of pruritus ani. Endocrine disturbances cause pruritus ani in an appreciable number of cases.

Observations on Hemorrhage of Scalp Wounds and Local Treatment of Burns. E. L. Kendig, Virginia M. Monthly **56**:219 (July) 1929.

Kendig prefers to use a 7.5 per cent solution of tannic acid in certain cases because this stronger solution will form a satisfactory crust in from ten to twelve hours. This is an advantage, as it makes the number of hourly applications less.

Treatment of Lupus Erythematosus with Gold. W. F. Manley, Virginia M. Monthly **56**:255 (July) 1929.

Manley used gold sodium thiosulphate in six cases of lupus erythematosus. In all five of the chronic discoid type there is a clinical cure. One patient with subacute disseminated erythematosus is still under treatment, and rapidly improving. In the five cases of the chronic discoid type in which treatment has been completed, the number of treatments given ranged from eleven to fifty-two. The duration of the disease does not seem to have any bearing on the number of treatments required. The only reaction noted in the chronic discoid type was a focal reaction in the affected areas with edema, erythema and tingling. One patient developed a polymorphous erythematous eruption which disappeared in

two weeks following cessation of treatment. In only one case was there a recurrence. This occurred three and a half months after a series of six injections and cleared up again after another six injections, and the patient has remained well ever since. In one case, tuberculous adenitis developed eight months subsequent to cessation of gold therapy but the lupus has not recurred.

Skin Regeneration and Cancer. R. J. Ludford, Brit. J. Exper. Path. **10**:193 (June) 1929.

Ludford asserts that repeated scarification of an area of the skin of the mouse does not result in an aberration of the process of repair, nor lead to the induction of cancer. An area of the skin that has been the site of repeated injury and repair is not more susceptible to the carcinogenic action of tar than the normal skin.

Erythema Nodosum in Primary Period of Tuberculosis. L. Bernard and J. Paraf, Ann. de méd. **25**:351 (April) 1929.

Bernard and Paraf report two cases of erythema nodosum that appeared during the primary period of tuberculosis. They consider these cases a new argument in favor of the frequently tuberculous nature of this condition.

Radaeli's Bacillus and Pemphigus. E. Antoniazzi, Riforma med. **45**:396 (March 16) 1929.

Antoniazzi recalls that, from 1906 to 1910, Radaeli took up the study of the etiology of pemphigus, and in five out of six cases he was able to cultivate from the cadavers (the spleen, the bone marrow, the liver and the blood) a small bacillus, which for various reasons he regarded as the etiologic agent of pemphigus. The same bacillus was isolated twice by Pasini in 1911 from the cadavers of seven patients with pemphigus, although the cultures in the living subjects were never positive. In 1914, Copelli isolated the bacillus in three cases of pemphigus, not only in the cadavers but also in the living subject. From the fact that Antoniazzi found the Radaeli bacillus present in a case of erythroderma, he thinks that this bacillus is, in all probability, only achromogenic, pyocyanogenic organism, and is not the etiologic agent of pemphigus. He admits that his deductions from a single case are, of course, not conclusive.

Use of Oxygen in Treatment of Carbuncle and of Furuncle. E. P. Fidanza and F. Carrillo, Semana méd. **36**:1145 (May 2) 1929.

The work done by Fidanza and Carrillo in twenty-nine cases shows that oxygen, when injected into a carbuncle or a furuncle, gives excellent results. The oxygen should be injected under moderate pressure for three or four minutes. This expels the toxic products of the necrotic destruction of the tissues. While the injection is being made, the openings through which the gas escapes should be covered with a piece of gauze to avoid dissemination of the pus. The presence of oxygen in the tissues is manifested by a bright red hue. After the injection, a piece of gauze, moistened with hydrogen dioxide, is applied. The treatment may be repeated two or three times a day, if necessary. The pain disappears at the first injection, and the fever is lessened; a crucial incision is avoided and the scar is small.

Dietetic Treatment of Tuberculosis of Skin. S. Bommer, München. med. Wchnschr. **76**:695 (April 26) 1929.

Bommer describes a salt-free diet for the treatment of tuberculosis of the skin. The principles of this dietetic treatment were first employed by Gerson. Sauerbruch and Herrmannsdorfer adopted them with slight variations. This regimen completely eliminates the use of salt in the preparation of foods. Meat is either entirely omitted or considerably restricted. The food is rich in fats but deficient

in carbohydrates. The daily ration contains about 90 Gm. of protein, 162 Gm. of fat and 222 Gm. of carbohydrate. To provide the patients with a sufficient supply of vitamins, they are served with plenty of fresh fruit and vegetables. The necessary fat is supplied mostly in the form of unsalted butter. Milk or milk gruels are given in comparatively large quantities. The author employed this dietetic treatment in a sanatorium for patients with lupus. The patients received food seven times a day, and twice daily they were given cod liver oil. Special care was taken to provide a sufficient variety in the meals, and to use other seasoning in such a manner as to prevent aversion to the salt-free diet. Most patients became accustomed to this regimen in about two weeks. At first the dietetic treatment was given alone; later it was combined with sun and light baths. When given in the proper way, these baths seemed to improve the good results of the dietetic treatment. Concerning the effects of the salt-free diet the author states that in from three to four weeks after the beginning of the treatment, the tuberculous lesions gradually become dry and covered with scabs. During the following three to six weeks these scabs fall off and the smooth scars underneath are hardly noticeable. In lupus, the brownish nodules and infiltrations disappear gradually. In many instances it could be observed that at times the healing process stopped for from four to five weeks, and after that it progressed again. The author asserts that the dietetic treatment leads to the complete healing of extensive tuberculous lesions. Because a longer period of time will be necessary for observation, no definite statement can as yet be made concerning the permanence of these results. Up to the present time, however, relapse has not occurred in those patients who left the sanatorium after having completely recovered.

TREATMENT OF FURUNCLE WITH CHAMBER PLASTER. W. MAYER, München. med. Wchnschr. **76**:838 (May 17) 1929.

Mayer points out that in the treatment of furuncle the proper dressing is of the greatest significance. To do away with the many shortcomings of the bandages employed formerly, the author perfected an ointment chamber plaster. With the application of this plaster the treatment of a funruncle is usually as follows: While the surrounding area is covered, the top of the furuncle is rendered anesthetic with ethyl chloride. After this an incision from 2 to 4 mm. in length is made in the furuncle. Following this the ointment chamber plaster is applied. It consists of a piece of adhesive plaster. In the center of this there is a circular opening which is covered with cellophan. Around this cellophan "window," on the adhesive side of the plaster there is a piece of felt. This felt not only serves for the formation of the chamber but also protects the skin immediately surrounding the furuncle, and thus prevents the development of secondary furuncles. The chamber is filled to about three fourths of its capacity with a specially prepared ointment (phenol crystals, 3 Gm.; triturated camphor, 6 Gm.; absolute alcohol, 1 cc.; sulphonated bitumen, 10 Gm.; wool fat, 20 Gm.; petrolatum, 10 Gm.; ointment base, 10 Gm.). After the plaster has been applied, the cellophan may be covered with a small piece of adhesive plaster. In order to determine whether it is necessary to clean the wound, the physician may press on the felt ring. If the pressure is not painful, the plaster may be opened by first removing the small piece of adhesive plaster. Following this, the cellophan is cut out with scissors. After the wound has been thoroughly cleaned with ether, the chamber is refilled with the ointment. Then it is again covered with cellophan and with adhesive plaster. From three to four days later, the furuncle is usually completely healed, and the whole plaster can now be removed. The following are the main advantages of the treatment with the chamber plaster: 1. The ointment remains fluid during the whole treatment; it has an anesthetizing effect and thus lessens the pain. 2. The ring of felt protects the skin surrounding the furuncle and prevents the formation of secondary furuncles. 3. In most instances one chamber plaster is sufficient. This eliminates the frequent changes of dressings. 4. The time necessary for the healing process is shortened.

EXPERIENCES WITH MAYER'S OINTMENT CHAMBER PLASTER. S. RUF, München. med. Wchnschr. **76**:839 (May 17) 1929.

Mayer's ointment chamber plaster was used by Ruf in 100 cases. The following instance convinced him that the treatment with the chamber plaster is really superior to other methods: In a patient who had two furuncles, one was treated with the chamber plaster, while the other was treated with moist compresses. The two furuncles were of about the same size. The one that was treated with the chamber plaster not only healed quicker than the one treated with compresses but also left a smaller scar. Ruf also states that he employed Mayer's chamber plaster not only for the treatment of furuncles but also in cases of ulcus cruris, for infected wounds and for various other suppurative processes. He particularly emphasizes the fact that this therapy alleviates the pain quickly.

AFTER TREATMENT IN INJECTION THERAPY OF VARICOSE VEINS. E. BOSCH, Schweiz. med. Wchnschr. **59**:482 (May 4) 1929.

In the treatment of 200 patients with varicose veins, Bosch employed the following method: Under manual compression of the vein, the patient is given an injection of from 5 to 10 cc. of a sterile 20 per cent solution of sodium chloride. Following this injection, cramps usually develop in the region of the vein. As long as they last, the patient should rest; after that he may walk. The control examination which is made several days later reveals a local swelling due to the artificially produced phlebitis. This condition, as well as the slight pains, generally disappears after several days or weeks. In order to secure permanent results with these injections, and to prevent a relapse, careful after-treatment is necessary. It is known that slight pressure on the skin is sufficient to press the blood into the deeper veins. To effect this practically, different methods may be employed. The author discusses the advantages and disadvantages of various bandages and of different types of rubber stockings. He considers the most advantageous bandage a stocking made of mercerized cotton. He employed it successfully not only in the after-treatment following injection or operation, but also in those cases in which such treatments were not advisable.

Society Transactions

MANHATTAN DERMATOLOGICAL SOCIETY

DAVID L. SATENSTEIN, M.D., *Secretary*

January-February-March, 1929

M. B. PAROUNAGIAN, M.D., *Chairman*

LUPUS VULGARIS TREATED WITH A GOLD COMPOUND. Presented by DR. PAROUNAGIAN.

S. L., a woman, aged 60, who was referred to the Bellevue Hospital Clinic on Nov. 15, 1923, at that time presented an extensive case of lupus vulgaris involving the greater portion of the face. The duration was ten years. She had been treated by various therapeutic remedies with no result.

On Oct. 26, 1927, the patient commenced treatment with injections of a gold compound, one each week, receiving twelve for the first course; as the urine showed albumin and casts, the treatment was discontinued for a while. The second course was started on March 14, 1928, at which time nine doses were given, and then the treatment was discontinued again. The next course was instituted on September 5, continuing to November 14, the patient receiving seven treatments more.

When she returned on November 21, the eruption was worse and the eyes were inflamed. She felt miserable and decided to discontinue treatment and was greatly discouraged.

When she returned on Jan. 4, 1929, the improvement was most pleasing. The eyes were clearer and the lesions of the face had healed, leaving some pigmented and some depigmented remains of scars.

DISCUSSION

DR. MACKEE: Whether this is a temporary or a permanent result, it is certainly a good result, undoubtedly due to the gold compound, either directly or indirectly. It seems as though there are enough data now collected on the use of gold preparations in various types of cutaneous tuberculosis to make the use of this drug in lupus vulgaris legitimate. There are some cases of lupus vulgaris in which the condition seems to yield to dietetic treatment, originated by the German School of pulmonary tuberculosis, and first tried in lupus vulgaris. It is claimed that good results have been obtained in both pulmonary tuberculosis and lupus vulgaris. Edgar Mayer is now experimenting with this method in cases of pulmonary tuberculosis at Saranac Lake. I have one patient with lupus vulgaris who is now almost cured, apparently as a result of the diet. It is a high vitamin, low sodium chloride diet.

SCLERODERMA. Presented by DR. PAROUNAGIAN.

A man, aged 39, an Armenian, first came under the presenter's care on Dec. 10, 1928, at which time he said that the skin disease on the left leg had begun four years previously, and that ever since that time, every month or two, his symptoms began with chills and rise of temperature to 103 F. or more, and that the left leg would swell and become painful. In three or four days the inflammation subsided but the discoloration remained.

The eruption was confined to the left leg, extending from the ankle to the knee. The skin was shiny, thickened and bound down. The Wassermann reaction was negative. The venereal history was negative.

DISCUSSION

DR. SATENSTEIN: I believe that this is a case of recurrent lymphangitis, each attack leaving the leg slightly larger and more infiltrated, due to more connective tissue proliferation.

DR. ANDREWS: I agree with Dr. Satenstein. The condition is not mentioned very much in the literature but occurs fairly often. We have two or three patients with the same condition under treatment, usually associated with ringworm between the toes. This patient has itching and a fissure between the great toe and the next toe, but no signs of ringworm. Sometimes the infection comes from around the nails. In the first case, the patient was treated with roentgen rays, the condition cleared up and the patient stayed well for a year or so, and then the condition returned. The best results, however, were with a combination of the roentgen rays and injections of streptococcus toxin. I have had good results in these cases.

DR. GILMOUR: I agree with the diagnosis of recurrent lymphangitis. I believe that Dr. Simmers has a preparation that would prove useful in lymphangitis of this type.

DR. MACKEE: I agree with the previous speakers. I think that this condition is a recurrent streptococcic lymphangitis. Many cases originate in a focus occurring as a fissure caused by dermatophytosis between the toes, or, in fact, any focus of infection. I agree that vaccine or antitoxin therapy is useful in the recurrent type, but the original focus should be removed if possible.

A CASE FOR DIAGNOSIS (CHANCROID?). Presented by DR. SATENSTEIN for DR. HARRIS.

C. C., aged 32, a salesman, had had the eruption since Dec. 1, 1928, at which time three small ulcerating granulomas appeared on the prepuce and had not disappeared. The following laboratory work had been done: Between Dec. 19, 1928 and Feb. 12, 1929, ten dark-field examinations were negative; four Wassermann reactions of the blood were negative, also cultures and stained slides for the Ducrey bacillus were negative. At no time were any enlarged glands noted. The patient never complained of headache, sore throat or any of the symptoms of secondary syphilis. He had been repeatedly examined for the possibility of a macular or papular rash, but none was ever present. Various antiseptics had been used as well as caustics without any benefit. The patient had received six ampules of tartar emetic intravenously with only slight improvement.

DISCUSSION

DR. OULMANN: I am rather inclined to regard the case as one of chancroid. There are no enlarged glands and no spirochetes as would be the case in chancre. It is difficult to cultivate the Ducrey bacillus.

DR. HOWARD FOX: I think that the burden of proof is on the one who would call this syphilis. The lesions were multiple, there was no trace of adenopathy or other signs of syphilis and the Wassermann reaction was negative. I should also add that the absence of local adenopathy was against the diagnosis of chancroid.

DR. MACKEE: If the history is reliable and arguing from the standpoint of primary syphilis, and allowing for delayed reaction, it is inconceivable that the Wassermann reaction can be negative three months after the appearance of the primary lesion. I cannot make a clinical diagnosis in this case, but, in spite of the fact that the case is well worked up by Dr. Harris, I think that more work should be done. A pathologic examination might be made; vaccination should be attempted, as well as additional direct microscopic examination.

DR. BECHET: I think the fact that the patient has had the lesion for two or three months, without a positive Wassermann reaction, or other symptom of syphilis, would eliminate that disease. It is difficult to make a definite diagnosis.

The patient is clean in his habits, but, in spite of this, the lesions may be chancroidal, and I should suggest such a possibility.

DR. ELLER: I feel more in favor of chancroid than syphilis because of the duration of the lesions without any enlargement of the glands, the negative Wassermann reaction, no signs of secondary syphilis and because chancroids are more likely to remain several months. The patient gave a history of having been exposed as much as two or three times a week.

DR. FRASER: I think that it is a pretty well established fact that it is unsafe to make a diagnosis of syphilis on the appearance of penile lesions, especially when such lesions are unaccompanied, as in this case, by other clinical or serologic signs of syphilis. I should suggest that we are possibly dealing here with an atypical type of herpes, but there should not be so much induration in herpes as is present in these lesions. I feel, as Dr. Fox does, that the burden of proof is on those who claim that the condition is syphilis.

DR. MACKEE: I can support Dr. Fraser's remark. I have seen ulcerative herpes progenitalis produce indurated ulcers lasting for several months, but in each instance the lesion had been treated with silver nitrate. I have never seen herpes produce long-enduring ulcers without the addition of some irritant.

DR. PAROUNAGIAN: One lesion is suggestive of chancre; the other two lesions impress me as chancroids. I wish it were possible to eliminate entirely the old belief that all multiple lesions are chancroidal. I could show any number of multiple chancres. Only yesterday I saw six distinct chancres on the penis. I showed a patient with fifteen distinct chancres at the Academy of Medicine. I have photographs of any number of cases of multiple chancres. Whereas I favor the diagnosis of chancroid in this case, I recall a recent case of a patient who came to us with several lesions on the genitals. We made many dark-field examinations and Wassermann tests which were all negative. The patient had not been treated. After two months' observation it was decided that the condition was not chancre but chancroid; it was treated locally and the patient disappeared. Two months later he returned with a roseola, and a 4 plus Wassermann reaction. Such cases do occur. I think that Dr. MacKee's suggestion is very good; I should treat him locally for chancroid and keep on with repeated Wassermann tests, vaccination and continued search for the Ducrey bacillus.

DR. HOWARD FOX: Are multiple chancres common in white people?

DR. PAROUNAGIAN: Multiple chancres are also common in white persons.

A CASE FOR DIAGNOSIS (URTICARIA PIGMENTOSA). Presented by DR. WALLHAUSER.

A girl, aged 4 years, presented an eruption involving the neck, chest and back, which had developed gradually over a period of about three years. The lesions consisted of circular and oval, brownish maculopapules, the size of a lentil seed. The surfaces were not perceptibly scaly, and each lesion was surrounded by an outlying areola of blanching.

DISCUSSION

DR. FRASER: The diagnosis, in my opinion, is urticaria pigmentosa.

DR. BECHET: I agree with Dr. Fraser.

DR. GILMOUR: There are not only macules but also papules changing to wheals with slight rubbing. My diagnosis is urticaria pigmentosa.

DR. MACKEE: I agree with the diagnosis of urticaria pigmentosa. The lack of scaling does not militate against the possibility of parapsoriasis as suggested by the presenter, because in the guttate or lichenoid type of parapsoriasis there is usually no exfoliation. In this case the lesions are yellowish-brown, pigmented macules, and they become distinctly urticarial when irritated.

DR. HOWARD FOX: I agree with the previous speakers. I rubbed two of the lesions and after friction saw them become distinctly urticarial.

DR. SATENSTEIN: I think that Dr. Wallhauser lost sight of an important fact, that the color in the urticarial lesion is a fixed color, whereas the color in parapsoriasis is due to dilatation and can be removed. Here, on pressure, there is no change of color. On that basis, rather than whether or not there are macules which can be rubbed into papules, I should be against the diagnosis of parapsoriasis.

DR. WALLHAUSER: Urticaria pigmentosa is clearly suggested by the character of the lesions, but when the patient was seen a few days ago I was unable to get any recrudescence by friction, and the mother said that no wheals were observed.

The point in differentiation suggested by Dr. Satenstein in calling attention to vascular involvement in parapsoriasis in contradistinction to the deposit of pigment in the tissues as demonstrated by the diascope is significant in establishing the diagnosis in this case as urticaria pigmentosa.

PIGMENTED NEVUS OF THE BLUISH TYPE. Presented by DR. HOWARD FOX.

E. K., a schoolboy, aged 12, had suffered from a lesion on the lower part of the bridge of the nose for two years. It was the size of a pinhead, slightly elevated, smooth, devoid of hair and of a bluish-brown tint. It had never been injured or treated. His mother thought that it had lately increased slightly in size. The patient was presented solely to discuss the question as to whether it was the physician's duty to advise removal or to allow it to remain under careful observation. It was not desired to raise the question of the method of treatment.

DISCUSSION

DR. SATENSTEIN: Looking at the lesion in good light, it did not have the bluish tones we are accustomed to see in forerunner's of melanoma. I consider this to be the ordinary pigmented nevus of the cutis type rather than epidermoid type, and perfectly safe to remove it. I should not suggest the method of using electrolysis at different sessions.

In all specimens I have examined of this particular type I have never seen one which became malignant. Whether the lesion is removed or not is simply a question of cosmetics.

DR. OULMANN: As long as there is a tendency for this lesion to grow, I should remove it. Such lesions stay unchanged sometimes for years and years with no reason to remove them, but when they show a tendency to grow I think that it would be wiser to remove them.

DR. MACKEE: I do not feel so optimistic as does Dr. Satenstein. While this is not a typical so-called blue-black mole, it has, nevertheless, a gunmetal rather than a brown color. I think that it is a potentially dangerous lesion. What Dr. Fox wants to know is whether it should be removed or kept under observation. I advise that it be kept under observation. The vast majority of these lesions are not dangerous unless irritated. I should watch the lesion carefully and if it shows evidence of activity of any kind I should excise it.

If it becomes necessary to destroy the lesion some drastic method should, in my opinion, be employed, preferably excision either with the high frequency current or with a scalpel. Many if not most of these lesions show, under the microscope, a fanlike downward spreading of the cells, the cells extending along the vessels and nerves. Therefore, the lesion may be considered a triangle with the apex at the skin surface. Dr. Satenstein has demonstrated this fact over and over again. The cells often extend well into the fat. For this reason the excision should be sufficiently wide at the surface, much wider below, and should extend down to the muscle.

DR. BECHET: I should not rely on the patient's history, but rather on my own observations. As Dr. MacKee has said, if the lesion is growing rapidly, it should be removed. As far as the method of removal is concerned, Dr. Fox knows them as well as we do. In fact, if I understand him rightly all he wishes to know is

whether or not the lesion should be removed. I should leave it alone if it presented no evidence of activity, but if it did, I should remove it at once.

DR. SATENSTEIN: In observing a good many of these cases, I find that the apparent growth of the lesion is not due to the growth of a nevus or any part of a nevus, but to inflammatory reaction about the lesion, due to irritation of one kind or another. If protected from injury until the present irritation subsides, it will be possible to determine whether or not it is growing.

DR. HOWARD FOX: The patient's mother was an intelligent woman, and the history of two years' duration was, I think, accurate. Whether it had increased somewhat in size was questionable. In my opinion such a lesion, as Dr. Pusey has pointed out, is a potential source of danger, though less so than if it were situated on the bearded region in an older person who shaved constantly. The question of causing a scar on the nose from radical removal made one hesitate to advise treatment unless this was felt to be imperative. I shall advise doing nothing for the present except to observe the patient carefully and watch for any sign of activity.

RADIODERMATITIS FOLLOWING TREATMENT FOR HYPERTRICHOSIS. Presented by DR. HOWARD FOX.

E. E., a woman, aged 32, an advertising agent, first visited the "Tricho" Institute in New York about November, 1926, for the removal of superfluous hair on the forearms. She received from fifteen to eighteen treatments given at first every two weeks and later every five or six weeks. The last treatment was given in the spring of 1927. In the summer of the same year she first noticed red lesions on the treated areas which slowly increased in extent after that. Examination showed a moderately severe telangiectasia and slight atrophy on the extensor surface of both forearms from the wrists to the elbows. Much of the hair which had fallen temporarily had returned. The patient went to the "Tricho Institute" on the advice of a hairdresser.

DISCUSSION

DR. BECHET: I see an average of two or three of these unfortunates a year.

DR. HOWARD FOX: The fact that hypertrichosis may be treated successfully by the roentgen ray is admitted by all. All dermatologists agree, however, that the danger of injury to the skin from the roentgen ray is too great to warrant the adoption of this method of treatment. I am particularly anxious to present cases of injury which have resulted from treatment by the "Tricho" people, as this concern now has a chain of institutions scattered all over the country. Their opportunities for harm are therefore proportionately great. I again urge, as I have on numerous occasions previously, that reports of injurious results be sent to Dr. Arthur J. Cramp of the Bureau of Investigation of the American Medical Association. If the dermatologists who see these cases do not take the trouble to report them, how can they expect that any curb can be put on the activities of advertising physicians using this improper method? My colleagues who neglect this duty are like the men who play golf on election day and neglect to vote, and later complain about the way the country is governed.

TINEA PROFUNDA (?). Presented by DR. SCHEER.

M. J. L., aged 40, a salesman, from the New York Post-Graduate Skin Clinic, had had the condition for seven months. It began as a tumor in the submaxillary region and under the chin, which at times discharged blood and pus spontaneously. At the time of presentation, across the submaxillary region was a raised nodular fluctuating mass about 4 inches (10.16 cm.) in circumference. The center was elevated 1 inch (2.5 cm.). Beneath it on the left side was a furunculoid lesion ½ inch (1.27 cm.) in diameter. Microscopic examination for fungi was negative. The patient received several roentgen treatments. Cultures were not made.

DISCUSSION

DR. OULMANN: The pus should be cultured. I do not regard the lesion as tuberculous.

DR. HOWARD FOX: Seven months is a long time for a tinea profunda to last and if the history is correct, I should doubt the probability of this diagnosis. The severe pyogenic types of ringworm are self-limited in a comparatively short time. I should suggest the possibility of a tuberculoma or "cold" abscess.

DR. BECHET: I had the patient under observation at the Skin and Cancer Hospital. Smears from the pus extracted by aspiration were negative for tinea. Hairs were also negative. The patient disappeared before a roentgenogram was made, and I should suggest to Dr. Scheer that this be done in order to determine the possibility of involvement of the bony jaw or teeth.

LUPOID SYCOSIS. Presented by DR. SCHEER.

W. R., aged 41, born in the United States, an ironworker, from the New York Post-Graduate Skin Clinic, had had the eruption for fifteen years, limited to the eyebrows, eyelashes and bearded region. The skin of the eyebrows was reddened and scaly, with crusted papules, the size of a pinhead. There was loss of hair and scarring. The eyelids were inflamed at the margins and presented an occasional papule. Practically all the eyelashes were gone. There was also ectropion.

A sharply defined erythematous and crusted area involved the upper lip and chin, extending laterally half way to the angles of the jaw and down on the front of the neck. The border of that area was made up of follicular papules some of which were crusted. The central portion of the area presented scattered crusted papules and areas of alopecia and atrophy. The patient had had numerous roentgen treatments. The pathologic histology was that of lupoid sycosis.

DISCUSSION

DR. BECHET: I do not believe that this case is one of lupoid sycosis. It is not limited entirely to the cheeks, with the superficial atrophic central areas, and peripheral folliculitis, so common in typical ulerythema sycosiforme of Unna. In my opinion, Dr. Scheer's case is an example of a clinical group characterized by pustular folliculitis originating in the scalp, spreading to the eyebrows, eyelashes, axillae and pubes, and consisting of pustules, scaling, crusting and permanent loss of hair. In severe cases ectropion occurs. This clinical group has probably the same etiologic factors as lupoid sycosis, but the clinical picture is an entirely different one.

DR. MACKEE: There are in the literature a number of examples of this condition diagnosed as lupoid sycosis. I have never been able to agree that they are pure cases of ulerythema sycosiforme. There is one lesion in each cheek that exhibits the characteristics of lupoid sycosis, but the remainder of the eruption is, to my mind, pyoderma — pustular folliculitis or sycosis vulgaris; in other words, ulerythema sycosiforme and sycosis vulgaris.

DR. HOWARD FOX: This appears to me to be a classic case of lupoid sycosis, precisely similar to many textbooks pictures of the disease. As I understand it such cases show, in addition to the scarred areas, other areas of the common type of sycosis.

BROMODERMA TUBEROSUM. Presented by DR. PAROUNAGIAN.

L. F., an American negro, aged 40, was first admitted to the Bellevue Hospital Clinic on Dec. 24, 1928. He had received ten intravenous injections for syphilis before coming to the clinic. On examination, a number of elevated, sharply outlined, vegetative lesions varying in size from that of a dime to that of a quarter, mostly on the lower extremities and a few on other portions of the body, were observed. The lesions had appeared about the beginning of December, 1928. The patient had been taking potassium bromide. The Wassermann reaction was repeatedly negative.

DISCUSSION

DR. HOWARD FOX: I do not recall having seen a case of bromoderma in a negro.

LUPUS ERYTHEMATOSUS DISSEMINATUS. Presented by DR. PAROUNAGIAN.

S. J., a man, aged 30, was first seen at the Bellevue Clinic on Jan. 22, 1929. The duration of the skin disease was six weeks. No history of venereal disease was obtainable. The lesions were located on the vertex (atrophied scar), on both cheeks, behind the ears, on both upper and lower extremities and also on the chest and back.

The lesions consisted of patches of various sizes and shapes, with erythematous borders; the centers of the lesions on the face were verrucous; most of the patches appeared to present some active lesions, depigmented and pigmented areas. He had been treated at various clinics with different applications, vaccines, etc., without improvement. The Wassermann reaction was negative on three occasions. A moderate amount of itching was present. The patient had received three injections of a gold compound.

DISCUSSION

DR. ROSEN: I should suggest the diagnosis of a nodular and squamous syphiloderm in spite of the fact that the lesions on the face and scalp are typical of lupus erythematosus. If one did not see the face and scalp but only the trunk, I do not believe it would be possible to make the diagnosis of lupus erythematosus on account of the extensive distribution and grouping of the lesions together with the spontaneous healing and markedly pigmented scars.

DR. MACKEE: I think that it is an unusually extensive case of the discoid type of lupus erythematosus.

DR. BECHET: The lesions on the back and scalp are typical of lupus erythematosus of the chronic discoid type, but the lesions on the trunk, particularly those on the thighs, are suggestive of an aberrant type of papulonecrotic tuberculid. Lupus erythematosus is frequently associated with papulonecrotic tuberculid, and the case under discussion seems to fit in this category.

DR. SATENSTEIN: I am more in favor of the diagnosis suggested by Dr. Rosen. The serpiginous and nodular character suggests a nodular syphiloderm.

DR. PAROUNAGIAN: The duration, absence of syphilitic history or syphilitic manifestations, symmetry and repeated negative serology do not favor the diagnosis of syphilis.

The location on both cheeks, behind the ears and on the scalp should favor the diagnosis of lupus erythematosus.

LUPUS VULGARIS AND EPITHELIOMA. Presented by DR. BECHET.

A woman, aged 50, had had lupus vulgaris on the nose for many years. She had received a great deal of roentgen treatment. The skin of the nose was atrophic and telangiectatic, and there was a crusted ulcer, the size of a split pea.

DISCUSSION

DR. FRASER: I do not feel like accepting the diagnosis of epithelioma without a histologic examination.

DR. SATENSTEIN: I agree with Dr. Fraser. The margin of the ulcer is not indurated. It may be lupus tumidans. I should not make a diagnosis of epithelioma without microscopic corroboration.

DR. HOWARD FOX: I do not think that a positive diagnosis can be made from the appearance of the crusts. They should be removed and a biopsy made. While not common, cancer is known to occur on lupus vulgaris, in perhaps from 1 to 2 per cent of cases. At a visit to the London Hospital, Dr. Sequeira showed

me twenty-five photographs of such cases, stating that he had also seen twice that number. His experience with lupus has been extensive.

DR. MACKEE: I think that the probable diagnosis is epithelioma and if not the chances are that epithelioma will develop if the lupus vulgaris is not destroyed. Dr. Fox has called attention to the frequency of epithelioma in lupus and that brings up the question whether the frequency is any greater now than before the advent of the roentgen ray. Epithelioma was fairly frequent in lupus vulgaris and lupus erythematosus before the roentgen ray was discovered. In this case it is difficult to ascertain whether the epithelioma is the result of the lupus, or of excessive roentgen treatment or both. Epithelioma occurring in the scar of lupus vulgaris or lupus erythematosus is not rapidly malignant because it develops in sclerotic tissue. Progress is slow and the lesion does not become invasive early. When the cells invade normal tissue, however, the tumor becomes highly malignant and rapidly invasive.

CARCINOMA OF THE TONGUE IN A SYPHILITIC PATIENT. Presented by DR. ELLER.

H. E., a woman, aged 49, born in the United States, from the New York Post-Graduate Skin Clinic, presented an ulceration of the tongue which showed complete destruction of more than an inch from the tip back. The duration was six months. The base of the ulcer was indurated. There was marked leukoplakia of the remainder of the tongue. The Wassermann reaction of the blood was strongly positive. This patient had received no therapy for the systemic syphilis or the ulcer of the tongue. A section of the ulcerating tongue tissue showed a prickle cell cancer. The lymphatics in the neck were enlarged. This case was presented to show the rapid destruction of tissue due to malignancy.

DISCUSSION

DR. SATENSTEIN: The question of taking a piece of tissue came up and it was decided that the clinical condition warranted further investigations to make the diagnosis. The tissue taken from the tongue showed infiltrating cancer and a tremendous amount of inflammatory tissue, with secondary infection. If we had gone one-quarter inch aside we probably would not have struck the neoplastic portion. That is often the history in a good many of these cases. The patient did not have gumma, she had leukokeratosis.

DR. SATENSTEIN: I think that it is a surgical case.

DR. PAROUNAGIAN: The majority of cases I have seen of cancer of the tongue usually begin on a syphilitic base, i. e., gumma turning to cancer.

LICHENOID SCLERODERMA. Presented by DR. FRANK FRASER.

M. S., a woman, aged 19, single, stated that the changes in her skin had begun three years previously with the appearance of a brown spot on the skin of the abdomen. When presented, the skin over the upper portion of the chest was smooth and shiny and difficult to pick up with the fingers. There was an exaggeration of the normal lines, and the consistence was harder than that of normal skin. Several localized areas on the back presented a similar picture. Dr. Fraser asked for suggestions as to therapy.

DISCUSSION

DR. OULMANN: In some of these cases, thyroid extract has been given with good results. On the other hand, sodium thiosulphate, especially when arsenic has been found in excess, has proved efficacious.

DR. WEISS: Possibly some of the members recall a case of scleroderma in a young girl, the bandlike lesion being across the forehead, who was cured under treatment with extract thyroid in small doses for three months.

DR. WISE: I suggest daily massage of the patient's lesions, using cold cream in cocoanut butter. I have observed good results from long continued massage.

PARAPSORIASIS (GUTTATE). Presented by DR. FRASER.

L. O. a woman, aged 20, single, stated that her eruption had first appeared five years previously. The lesions were located on the trunk and limbs and consisted of round, red macules, covered by fine scales, and ranging in diameter from 1 to 6 cm. There had never been any itching. The results of the microscopic examination fitted into the diagnosis of parapsoriasis.

PARAPSORIASIS (GUTTATE). Presented by DR. ANDREWS.

S. R., a woman, aged 44, stated that her eruption had begun on the wrists when she was 8 years of age and had gradually spread over the entire body. She had had ultraviolet ray therapy for one year prior to presentation, and the eruption had cleared up completely, but only temporarily.

On the trunk, especially on the sides, and on the upper part of the arms and on the thighs, were guttate, superficial, slightly scaly, bright brown, yellowish and pink macules and papules.

DISCUSSION

DR. WALLHAUSER: Both cases presented the characteristic pale, pinkish macules with pinpoint lichenoid elevations and pityriasic scaling which, with the history of long duration, should establish the diagnosis of guttate parapsoriasis.

DR. ROSEN: These cases are interesting and instructive on account of their close resemblance to secondary syphilis. Unless one takes into consideration the duration of the condition, it is often difficult from the clinical appearance to make a differential diagnosis.

DR. FOX: Dr. Fraser asked for therapeutic suggestions. I merely quote results published by Dr. Chipman of San Francisco, who treated three patients with parapsoriasis, representing one each, of the three types; he treated them all with the quartz lamp and obtained temporary results, at least.

LOCALIZED ARGYRIA. Presented by DR. OULMANN.

The patient, a man, aged 62, had been treated twenty-one years previously for some trouble of the lachrymal duct. Silver stilets had been inserted, and a 10 per cent argyrol solution had been injected by a dropper. Shortly thereafter, the entire region of the right eye and part of the left eye became brownish black. Later on, an incision was made at the right inner canthus, which caused bleeding. The upper part of the right eye became free from the discoloration, and also most of the left eye, while the discoloration of the lower part and of the inner canthus of the right eye, where the incision had been made, remained. In time, the color changed and took on a greenish-black hue, such as that seen in argyria.

DISCUSSION

DR. FOX: It is rather alarming to know that argyria may follow the use of argyrol, a drug that is not supposed to cause it. Cases of the kind are, I believe, on record.

A CASE FOR DIAGNOSIS (PSORIASIS?). Presented by DR. WISE.

M. S., a married woman, aged 62, a patient from the New York Post-Graduate Skin Clinic, had had an eruption for five years. A recent exacerbation was of four months' duration. She presented an inflammatory eruption of the palms and soles, consisting of circumscribed, hyperkeratotic plaques with well defined borders, associated with considerable scaling and fissuring of the palms. The back of the hands and feet exhibited scaling, erythematous, macular lesions, varying in size from ¼ to 1 inch (0.61 to 2.5 cm.) in diameter, resembling psoriasis. On the forearms, extending up to the elbows, were disseminated maculopapular and scaly lesions, erythematous and pruritic, resembling the lesions of acute lupus erythema-

tosus. The toes presented an advanced form of maceration and desquamation, as seen in infections with ringworm. There were also psoriatic plaques over the patellae. The patient complained bitterly of itching of the lesions. The general health was good.

DISCUSSION

DR. WALLHAUSER: I am inclined to the opinion that the patient presented two separate conditions. The lesions on the elbows were characteristic of psoriasis. Regarding the involvement of the hands and feet, we should await the result of treatment.

DR. OULMANN: I think it is dermatophytosis with circumscribed lesions of some dimensions.

DR. ANDREWS: I am inclined to agree with Dr. Oulmann.

DR. FOX: I think we would have a better idea if a microscopic examination had been made. My guess would be the same as that of Dr. Andrews and Dr. Oulmann, i. e., dermatophytosis.

DR. ROSEN: Psoriasis of the palms and soles resembles dermatophytosis, and it often requires careful analysis to rule the latter out. In this instance, the absence of vesicles, the marked and persistent keratosis, the sharply outlined lesions and the resistance to local treatment, with the presence of psoriatic lesions elsewhere, all favor that diagnosis.

XANTHOMA DIABETICORUM. Presented by DR. ROSEN.

J. C., a man, aged 43, born in Italy, appeared at the Post-Graduate Hospital Skin Clinic, on Feb. 25, 1929. He stated at that time that he had had an eruption on the body for the past year. On examination, he presented over the buttocks, lower extremities and extensor surfaces of the upper extremities and lower abdomen numerous discrete, pinhead to bean sized, hard, yellowish and reddish, raised lesions. Some of them were grouped together to form larger patches.

Examination of the urine showed 2 per cent sugar with a specific gravity of 1.032. Chemical examination of the blood showed sugar 0.185 per cent and cholesterol 0.280 per cent.

XANTHOMA TUBEROSUM MULTIPLEX. Presented by DR. ROSEN.

M. L., a woman, aged 47, born in England, appeared at the Post-Graduate Hospital Skin Clinic on Feb. 18, 1929. She stated that she had had an eruption for seven years. On both elbows there were grouped yellowish-red, nodular lesions. There were also many scattered, sharply defined, pea-sized lesions, irregular in outline and of a chrome yellow color. Pea-sized and cherry-sized, hard, nodular lesions appeared on the backs of the fingers and in the palms of the hands. There were similar patches over the left knee, and lesions were also present on the feet and soles.

Chemical examination of the blood showed sugar 0.088 per cent and cholesterol 0.435 per cent. Biopsy was undertaken but had not been reported.

DISCUSSION

DR. OCHS: A child was treated by Dr. Berkowitz with palladium, at the suggestion of Dr. Mount, with complete recovery. Since that time, I had a patient treated by that method, without result.

KERATOSIS PLANTARIS HEREDITARIA IN MOTHER AND TWO DAUGHTERS. Presented by Dr. Fox.

Three patients, a mother and two daughters, were presented. The mother, Mrs. D., was aged 44; the older daughter, A. D., 24, and the younger daughter, D. D., 12. The disease had been first noticed in the mother at the age of 4½, in the older daughter at the age of 3½ and in the younger daughter at the age

of 2. The mother was one of eight children (five boys and three girls). Her father was living and well at the age of 75. Her mother had died of rectal cancer at the age of 60. Neither of these parents nor any of the four grandparents had ever suffered from a similar involvement of the skin. There had not been a consanguineous marriage in the case of the mother, of her parents, or of her grandparents. In addition to her two daughters who were affected, Mrs. D. had a son, aged 14, who was free from the disease.

The location and the appearance of the lesions were strikingly the same in all three patients. The lesions were confined almost entirely to the bearing surface of the feet (toes, ball of the foot and heel). They consisted of yellowish, warty or callous-like growths of varying thickness. They had always caused more or less discomfort in walking, the mother stating that she was "always conscious of her feet." The palmar surface of one or more of the fingers was affected in each of the patients, but to a slight degree, being most evident in the mother. In her case there were a few pea-sized lesions most marked on the index finger. The older daughter showed a callosity of the right thumb, the younger a slight verrucosity at the border of one of the nails and a few warty lesions of the fingers.

Treatment had never produced any permanent result, the greatest relief being obtained by paring the lesions. There had been no result from fractional doses of the roentgen ray given weekly for three months, and thyroid extract for several months had not caused any benefit.

All the patients were well nourished and apparently in good health. They were all born in the United States.

DISCUSSION

DR. OCHS: The familial type is rather rarely seen. I agree with the diagnosis. These cases suggest the mal de Meleda.

DR. TULIPAN: Keratodermias of this type have been found among the inhabitants of the Island of Meleda, in the Adriatic, where they intermarry. The term mal de Meleda has been applied to the condition when found in the inhabitants of this island.

DR. FOX: Temporarily one can help the patients by paring the lesions or by treating them with the roentgen ray, radium or salicylic acid. The condition is, however, admittedly incurable.

SARCOID. Presented by DR. ROSEN.

A. S., a colored woman, aged 29, born in the United States, appeared at the Post-Graduate Hospital Skin Clinic on Feb. 10, 1929, stating that she had had an eruption for fourteen years. On examination, she was found to have an egg-sized, sharply defined, nodular patch, which was smooth and slightly raised. Many pinhead and pea-sized, raised lesions surrounded the lower eyelids. An irregular, sharply outlined patch, the size of a dollar, composed of hard, smooth nodules, was present on the outside of the right arm. A similar patch was on the left cheek under the left eye. There were an almond-sized patch on the neck and an elongated patch on the outside of the upper left arm. A similar patch was present on the left shoulder, the lesions being slightly tender to the touch.

The nasal smear was negative for leprosy. The Wassermann reaction was also negative. Biopsy revealed sarcoid (G. Satenstein).

DISCUSSION

DR. FOX: The clinical appearance of the infiltration of the face suggests leprosy, though this can be ruled out by the entire absence of other manifestations of this disease. Clinically, I should therefore think sarcoid the most likely diagnosis, which I understand was confirmed by the microscope.

DR. ANDREWS: I agree with the diagnosis of sarcoid. The lesions have the appearance of granuloma annulare, but this diagnosis is excluded by the long duration.

DR. SATENSTEIN: The tissue here is composed of distinct epidermoid tubercles surrounded by lymphocytes; there is no inflammatory process, no connective tissue cells and no fatty degeneration of the cells as found in leprosy. This is the superficial type of sarcoid, although some of the nodules were in the deep cutis. To make an absolute diagnosis of leprosy, if there were ulnar enlargement, we should have to demonstrate the presence of organisms in the tissue.

FOR DIAGNOSIS (PRURIGO NODULARIS?). Presented by DR. ROSEN.

C. F., a colored woman, aged 23, born in the United States, appeared at the Post-Graduate Hospital Skin Clinic on March 11, 1929. She stated that she had had an eruption on the arms and legs for nine months. On the extensor surfaces of the upper extremities there were discrete pinhead to pea-sized, well defined, raised, brownish and wartlike, infiltrated, round lesions. On the lower extremities, the lesions were much larger, harder and more wartlike in appearance. The Wassermann test and the biopsy had not been completed.

DISCUSSION

DR. WISE: The lesions clinically resemble prurigo nodularis.

DR. SATENSTEIN: I do not think any one can make a clinical diagnosis here. There are a number of conditions that have to be considered: prurigo nodularis, papulonecrotic tuberculid and leukemia. We examined the patient carefully and found no lesions suggestive of lichen planus.

DR. OULMANN: I favor prurigo nodularis.

DR. FOX: I agree with Dr. Wise that the eruption looks like prurigo nodularis, except that there are practically no scratch marks. The patient also says that itching is slight. It is at least a prurigo-like eruption and might be due to leukemia. I saw no suggestion of papulonecrotic tuberculid. A careful examination for scars failed to show a single one on either the upper or the lower extremities, which would be sufficient to exclude that disease.

TUBERCULID TREATED WITH A GOLD COMPOUND. Presented by DR. PAROUNAGIAN.

J. B. had been presented at the January meeting of this society at the beginning of treatment. He had been given twelve injections of a gold compound from Dec. 4, 1928, to Feb. 19, 1929. The lesions had entirely disappeared and no new ones had been detected.

CONGENITAL SYPHILIS. Presented by DR. PAROUNAGIAN.

J. R., a woman, aged 19, came to the Bellevue Hospital clinic on June 20, 1928. The Wassermann reaction was four plus. Her parents were living; the mother had had one stillbirth and three miscarriages. There was marked erosion of the incisors and canines, tubercle of Carabelli, high vault, protruding forehead, and an irregular and imperfect hairline.

PHENOLPHTHALEIN DERMATITIS. Presented by DR. PAROUNAGIAN.

W. B., a man, aged 34, entered the Bellevue Clinic on March 4, 1929. Examination revealed bullous lesions of the throat, palate, lips and glans penis, and also dark-brownish discolorations on the lower lip and backs of the hands. The Wassermann reaction was negative. The duration of the eruption was three days. The patient had had a similar attack two years previously. Drugs containing phenolphthalein had been taken the day before the attack.

To substantiate the diagnosis, the patient was requested to take the drug on Sunday, March 10, and on Monday afternoon he was again seen. He stated that about three hours after the ingestion of the drug he felt itching and stinging on various parts of the body, and that finally new lesions appeared. He showed a number of round, brownish patches on the hands, the face and lips and on the shaft of the penis.

DISCUSSION

DR. WISE: I agree with the diagnosis. I have seen at least three cases beginning with vesicles.

LUPUS ERYTHEMATOSUS DISSEMINATUS. Presented by DR. PAROUNAGIAN.

S. J. had been previously presented before the society at the meeting of February, 1929, and after long discussion some doubt was expressed about the diagnosis, a diagnosis of tertiary syphilis having been made by some of the members. A suggestion was made that the presenter should give the patient antisyphilitic treatment, that a biopsy be made and that the patient be presented at the next meeting. The patient had been given four injections of 0.45 cm. each of neoarsphenamine. There had been no improvement in the lesions. Dr. Satenstein, who examined the sections, reported that the histology was that of lupus erythematosus.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

R. H. RULISON, *Secretary*

Regular Monthly Meeting, March, 1929

I. ROSEN, *Chairman*

CASE FOR DIAGNOSIS (PHENOLPHTHALEIN DERMATITIS?). Presented by DR. GROSS.

H. W. M., a colored boy, aged 12, born in the United States, had had an eruption for more than two months. It caused mild itching. When he was first seen in the Vanderbilt Clinic, February 25, the eruption was on both arms, and consisted of numerous circinate lesions showing distinctly raised borders and pigmented slightly scaly centers. These lesions varied in size from that of a dime to that of a quarter. In the axillary region and on the chest, the eruption was barely raised, and a large area of pigmentation was seen in the center. A slight scaliness was present in these also. On the lower part of the chest and on the abdomen there were numerous pigmentations each the size of a nickel. The back and the legs were completely free. The Wassermann reaction was negative; repeated examinations for fungi showed none. The patient gave a history of taking phenolphthalein occasionally.

DISCUSSION

DR. ELLER: I think the eruption is due to a drug and most probably to phenolphthalein.

DR. POLLITZER: I suggest the possibility of lichen planus; it should not be ruled out at least without a biopsy.

DR. ABRAMOWITZ: The eruption is more like an atypical pityriasis rosea—atypical, because of the distribution on the arms and neck with hardly a lesion on the trunk. Another possibility is a generalized tinea. I have seen described some eruptions resembling pityriasis rosea following the use of some of the heavy metals, i. e., gold or arsenic, but I am not acquainted with any eruptions due to phenolphthalein that look like this. I do not think that because a patient

with an eruption has taken phenolphthalein one must construe it as due to that drug. He should receive a test dose to see if the eruption flares up. Further observation and also a biopsy are necessary to confirm or exclude the possibility, also, of lichen planus.

DR. GROSS: The patient is presented with the diagnosis of toxic erythema possibly due to a drug. This is the only diagnosis we could make considering our repeated failures to find a fungus. As to lichen planus, the extremities certainly suggest it, but the lesions on the chest show a confluence and widening with central healing such as was never observed in lichen planus. This also rules out pityriasis rosea. Of course, we are not dealing with a typical eruption due to phenolphthalein. But we have seen different clinical conditions due to the drug.

A CASE FOR DIAGNOSIS (ARSPHENAMINE DERMATITIS?). Presented by DR. ROSTENBERG.

E. F., a man, an attendant at a gasoline station, contracted syphilis four years previously for which he received treatment for two years, consisting of a total of eighteen injections of arsphenamine and twenty-four of mercury. After this the Wassermann reaction was negative. He was free from all symptoms until January, 1929; then a large gumma developed on the left side of the tongue. The Wassermann reaction was now four plus. He was immediately treated with arsphenamine, and the eruption developed after the third injection. He stated that the same eruption had occurred when he had had his previous treatments.

In the region of the index finger and thumb on both hands there was an absolutely symmetrical eruption composed of papules varying in size from that of a pinpoint to that of a split-pea, and in color from dark red to purplish. In places they had become confluent, forming rings and plaques. There was moderate itching.

DISCUSSION

DR. CHARGIN: The type of eruption observed in this case, but more general in extent, has certainly been observed following the administration of arsphenamine, eruptions suggestive of lichen planus.

DR. ELLER: I venture the diagnosis of dermatitis venenata due to gasoline and other petroleum products.

DR. ROSTENBERG: I cannot agree with the suggested diagnosis of dermatitis venenata. There was at no time any vesicular or acute stage suggesting dermatitis. Furthermore, the patient had always handled gasoline, whereas the present condition developed after he had received arsphenamine.

LUPUS ERYTHEMATOSUS IN CHILD. Presented by DR. BECHET.

J. J., aged 12, for a year had patches on the face covering most of the cheeks and nose. These patches were reddish, raised and infiltrated and, in certain places, particularly beneath the left eye, they were slightly scaly, hyperkeratotic and atrophic. The margins of the plaques were sharply defined. The patient's general health was good.

DISCUSSION

DR. CHARGIN: With regard to lupus erythematosus in young persons, I may report that we had under observation in the service of Dr. Goldenberg, at the Mount Sinai Hospital, a boy between 3 and 4 years of age, who showed typical lupus erythematosus of the face.

LINEAR LICHEN PLANUS. Presented by DR. CANNON.

C. C., aged 47, born in Russia, a widow, and practical nurse, had a rash that had broken out rather suddenly on the left upper part of the chest about six weeks previous to presentation. It itched slightly, and sometimes during the next two weeks a rash appeared on the left arm and persisted. The patient had had no treatment.

Examination showed on the left upper part of the chest a crescent-shaped group of flat, shiny, violaceous papules, 6 by 2 inches (15.3 by 5 cm.) in size. Extending down the flexor surface of the left arm from the shoulder to the wrist was a roughly linear lesion consisting of grouped, flat-topped, violaceous papules. On the extensor surface of the left elbow was also a palm-sized area of similar, grouped lesions. No other spots were present on the body or on the mucous membranes.

DISCUSSION

DR. ABRAMOWITZ: I agree with the diagnosis. I would like to suggest that a better terminology would be zosterform lichen planus, in view of the distribution in relation to the nerve.

SCLERODERMA. Presented by DR. HOPKINS.

G. G., a man, white, aged 30, born in the United States, a glassblower, had scleroderma. The history revealed that the condition had begun after the patient had been working on special vacuum lamps. He believed that in this work he had been exposed to arsenic fumes. In December, 1926, he had become acutely ill with some mental symptoms, fever and an acute eruption diagnosed as scarlet fever. During his convalescent period in January, 1927, he noticed stiffness of the face extending to the trunk and arms, and which had gradually become more severe until January, 1928; since then there had been a slow but distinct spontaneous improvement. Medical examination gave negative results. A roentgenogram of the sella turcica appeared normal.

SCLERODERMA TREATED WITH SODIUM THIOSULPHATE. Presented by DR. FEIT.

A man had had an eruption for seven years. His general health was good. The eruption consisted of an oblique band running from the right thumb to the middle of the forearm. The band was of ivory color and hard consistency, and showed telangiectasia. The whole region of the elbow and the whole dorsal surface of the left hand showed an atrophic skin which in some places was so thin that the underlying veins were visible. The atrophic skin was bluish-red and not unlike the skin seen in acrodermatitis chronica atrophicans. A similar condition was present on the dorsum of the right foot, reaching about 3 inches (7.6 cm.) above the ankle. The skin of the last described region was always tight and scaly. The patient had been for almost three years under antiarsenical treatment consisting of injections of from 0.5 to 2 Gm. of sodium thiosulphate. Examination of the urine showed a large amount of arsenic. The patient noticed a change in the tightness of his skin about three weeks after the commencement of these injections, together with severe neuritis, which probably was caused by the arsenic liberated from the tissue and circulating in the blood.

DISCUSSION

DR. SCHEER: Dr. Feit's patient has two diseases, i. e., scleroderma and acrodermatitis chronic atrophicans. The latter was particularly pronounced on the dorsal surface of one hand and also on the lower extremities.

DR. LEVIN: I believe that Dr. Feit's patient presented the characteristic lesions of acrodermatitis chronica atrophicans, while Dr. Hopkins' patient showed typical scleroderma.

DR. COMBES: Do I understand that the presence of arsenic was used to differentiate between acrodermatitis and scleroderma?

DR. MCCAFFERTY: Some cases of scleroderma have been reported in which arsenic was found in the urine. Scleroderma has therefore been attributed in some instances to the presence of arsenic in the system. Sodium thiosulphate is given to liberate the arsenic. In Dr. Feit's case, which is shown as one of scleroderma improving with administration of sodium thiosulphate, it appears

that arsenic may be the etiologic factor. Dr. Wise, a few years ago, clearly pointed out the differences between scleroderma and acrodermatitis chronica atrophicans.

DR. POLLITZER: As a matter of historical interest, about twenty-five years ago, a series of cases of scleroderma was reported in which there was an obvious excess of arsenic in the system. Further experience, however, showed that most cases of scleroderma give no evidence of arsenical intoxication. If the arsenic in some cases has any effect in relation to the disease, it must be an indirect effect, for instance, through the thyroid. Arsenic is therefore only one of several possible causes of scleroderma.

DR. BECHET: I am in accord with Dr. Scheer's opinion. Dr. Feit's patient has typical acrodermatitis on his hands. The skin is dusky red, thin and translucent. It is not unusual to see scleroderma and acrodermatitis in the same patient.

DR. FEIT: These cases are not rare. I have seen several of them here and abroad and always the question came up as to whether it was scleroderma or acrodermatitis chronica atrophicans. The only way to determine this is by biopsy. It seems some of them are scleroderma in the atrophic stage, simulating acrodermatitis. I cannot conceive of all these patients having both conditions. As regards arsenic, there seems to be some misunderstanding. It is not the direct cause, but is an indirect cause by reason of a toxic effect on the vegetative nervous system and the endocrines.

DR. ELLER: About six years ago, Dr. Fred Wise, in an article on the subject of acrodermatitis chronica atrophicans and scleroderma, differentiated between the two diseases. First, he held that only about one third of the cases of acrodermatitis chronic atrophicans reported in the literature presented evidence of sclerotic skin; that the other two thirds of the cases were cases of uncomplicated atrophia cutis. Second, he said that not all cases of scleroderma end with atrophy, and the fact that some terminate in complete atrophy, does not mean that this disease, when appearing on the extremities, bears any relation to acrodermatitis chronica atrophicans. If one follows the clinical course of each of these diseases, even in cases in which they appear on the extremities, they can be differentiated. Acrodermatitis chronica atrophicans in its atrophic stage presents a smooth, soft, appearance; the skin may be lifted in fine folds (anetodermia) and is a peculiar color. These characteristics are in great part lacking in the atrophic end-stage of scleroderma. Scleroderma bears no relation to acrodermatitis chronica atrophicans, as the former is a sclerosing process and the latter an atrophying dermatitis.

HYPERPLASIA OF SEBACEOUS GLANDS. Presented by Dr. Feit.

L. H., a man, aged 62, born in Roumania, had scattered over the forehead numerous yellowish-red, pinhead-sized nodules, which had been present for many years.

Biopsy showed a thinned epithelial layer with intercellular edema, and a corium in which there was edema with an infiltration of new-formed fibroblasts and occasional lymphocytes, particularly about the blood vessels. The infiltration was also prominent about a large collection of sebaceous glands that constituted the major part of a tumor removed from near the outer canthus of the left eye.

DISCUSSION

DR. MCCAFFERTY: These small lesions on the forehead are clinically intimately connected with the sebaceous glands. Dr. Feit and I were interested in the exact histologic picture of the lesions; therefore we had a biopsy done on one of them. The histologic picture was simply that of hyperplasia of the sebaceous lobules. This makes its classification that of adenoma sebaceum, which was first described by Balzar and Menetrier. This histologic picture is in contradistinction to that which Pringle described which was of an increased amount of connective tissue, hypertrophy of the sebaceous gland lobules and dilatation of the small venules.

Hallopeau gives another interesting classification, but I will not go into it here. Therefore, while Dr. Feit's case histologically presents the picture of Balzar's adenoma sebaceum, yet I do not believe that these cases, which occur rather frequently in elderly people, should be dignified with the name adenoma sebaceum (Balzar), because of the confusion with adenoma sebaceum (Pringle), which we most frequently associate with children. I believe that Dr. Feit's case should better be spoken of as an adenomatous hyperplasia of the sebaceous gland.

DR. BECHET: I agree with Dr. McCafferty. This condition is extremely common, especially in older people, and consists apparently of hyperplasia of the sebaceous glands.

DR. FEIT: The main difference between Balzar's, Pringle's and Darier's adenoma sebaceum and that presented tonight is the clinical appearance; histologically there is hyperplasia or hypertrophy of the sebaceous glands with more or less formation of blood vessels or fibrous tissue.

PSORIASIS IN A NEGRESS: Presented by DR. COMBES.

S. B., a negress, aged 27, born in North Carolina, of full-blooded negro parents, had had an eruption on her arms and legs for four months. The lesions were erythematopapular, varying in size to 3 cm. in diameter and covered with loosely adherent, silvery, micaceous scales. They were located on the legs and arms with a preference for grouping about the knees and elbows. Some of the scales on the thighs had been removed by ointment, leaving slightly depigmented areas.

PSORIASIS IN A MULATTO. Presented by DR. FEIT.

L. G., a woman, aged 25, was from South Carolina. The family history was negative. The grandfather was a white man. On the back of the hands of the patient were typical psoriatic lesions of the nummular type, dry, and covered with silvery scales. Scattered over the body were similar lesions, in places forming large patches each about the size of the palm. Guttate lesions were also present. The nails were free. The duration was four years.

PAPULONECROTIC TUBERCULID (?). Presented by DR. ROBINSON.

P. B., aged 26, a dishwasher, a patient, from the Vanderbilt Clinic, gave a history of having had an occasional papule on the hands and knees for twenty years. An acute outbreak had occurred about two months prior to presentation in which the lesions extended from the wrists to the elbows. The patient's mother had had similar lesions until she was 30 years of age; also a brother and a sister. There was no history of tuberculosis in the family. The patient had always been in good health.

On the hands and elbows the patient presented numerous, red pinhead-sized, hard papules covered with adherent scales. The papules on the back of the hands and wrists were more or less acute, showing some erythema; others showed each an indolent necrotic center. On the forearms were the cicatricial remains of former lesions. Guinea-pigs inoculated with material from the lesions showed no reaction.

Biopsy disclosed a perifolliculitis and folliculitis without tuberculosis.

DISCUSSION

DR. ELLER: I think that this is a case of acne varioliformis. The patient has had lesions on the forehead and scalp.

DR. SCHEER: In addition to the lesions on the forearms, similar lesions appeared in the occipital region. With the duration of twenty years, the absence of pitted scars, which should be expected in numbers after numerous attacks, the location of the lesions and the absence of necrosis in the centers of the active ones militate against the diagnosis of papulonecrotic tuberculid. I suggest Bockhart's impetigo, a chronic persistent folliculitis of the extremities and the scalp. I had a similar case in a girl aged 10½ who had an eruption of eight years' duration.

DR. MCCAFFERTY: This patient was seen by several of us in daylight. She presented typical necrotic papules, superficial ulcerations, scarring and pigmentation. Those of us who saw her all agreed on a diagnosis of papulonecrotic tuberculid. At the time of examination, we did not see any typical yellowish pustules such as those described by Bockhart; therefore, I think the case should be presented as that of papulonecrotic tuberculid.

ADDISON'S DISEASE. Presented by DR. CANNON.

Mrs. J. D., aged 55, white, born in Germany, was admitted to the City Hospital on Sept. 16, 1928, because of marked asthenia and extreme pigmentation of the skin. Her past history had been negative until about one year prior to admission; then she began to complain of lack of energy, and the skin grew darker. She had not had pediculosis or any other parasitic involvement of the skin.

She proved to be a fairly well nourished, but extremely weak woman, whose mind appeared vague and from whom answers were elicited with difficulty. She showed diffuse, dark brown pigmentation of the skin, most marked on the covered portions of the body and least severe on the face and hands. Throughout the pigmented areas were numerous circular white atrophic marks, which were probably the result of scarring from scratching. There was generalized enlargement of the superficial glands. The spleen was palpable 2 cm. below the right costal margin. The liver was barely palpable. There was a marked sense of resistance along the left rectus muscle, but no underlying mass could be made out. A roentgenogram of the chest and of the gastro-intestinal tract disclosed no pathologic condition. Biopsy of the skin showed a moderate increase in epidermal pigment, but no pigment in the underlying cutis. The blood pressure was 100 systolic and 70 diastolic. Urea nitrogen was 21 mg.; sugar, 10 mg. The Wassermann reaction was negative. The percentage of hemoglobin was 50, the red cell count 3,500,000, the white cell count 13,700, of which the polymorphonuclears constituted 67 per cent and the lymphocytes 27 per cent.

DISCUSSION

DR. MCCAFFERTY: I agree with the diagnosis of Addison's disease. The pigmentation and the low blood pressure fit into the picture of suprarenal dysfunction. However, the mucous membranes are not pigmented, and this is almost always present in Addison's disease.

DR. ABRAMOWITZ: This marked melanosis is unusual in Addison's disease. It does not fit into bronze diabetes, arsenical pigmentation, or vagabonds' disease. An unusual feature is the numerous linear, circular and oval depigmented spots, as of previous lesions of dermatitis herpetiformis, healed, perhaps, with arsenic.

DR. GROSS: This is a good example of rather extensive vagabonds' disease. We have to keep in mind that pigmentary changes in vagabonds' disease are not entirely due to external irritation by insects and scratching. The slight edema of the face and the obvious anemia suggest a bradycardic edema not infrequently seen in undernourished people.

DR. BECHET: Dr. Abramowitz' suggestion of arsenic as a possible etiologic factor in the pigmentation should be considered. I have recently observed an identical picture in a woman with pemphigus, who had been taking arsenic for a long time. The pemphigoid lesions had completely disappeared, and the body was covered with areas of deep pigmentation, with normal skin between, giving a curious lacelike effect.

DR. MCCAFFERTY: I do not recall having seen any case of vagabonds' disease in which there was pigmentation of the face. The pigmentation in vagabonds' disease is limited solely to the trunk and extremities.

DR. CHARGIN: The asthenia, the low blood pressure and the generalized pigmentation, evidently with melanin, suggest that we are dealing with disease of the suprarenal glands, the nature of which may be determined by further study.

DR. CANNON: The diagnosis of Addison's disease was made chiefly by exclusion. We took into consideration pediculosis, but this was excluded because of the universal pigmentation, its dark color and its slow increase. There was no history of the patient's having received arsenic, and her blood, urine and skin gave no indication of this drug. Because of her marked mental depression, general weakness, low blood pressure and pronounced pigmentation of the skin, we thought we were justified in making a diagnosis of glandular disorder, most likely suprarenal.

LUPUS MILIARIS DISSEMINATUS. Presented by DR. CHARGIN.

N. E., a man, aged 45, born in Greece, married, a laborer, had been in the United States for seven years. His health had always been good; he denied having had any form of skin trouble. There was a questionable history of syphilis, but the Wassermann reaction at the time of presentation was negative. He denied having had antisyphilic treatment. The eruption, which was of two months' duration, was limited to the face. It had appeared first on the forehead, then on the nose and in the course of weeks, on the cheeks. The lesions were especially numerous on the forehead, the nose and the adjacent part of the cheeks and the chin. There were numerous lesions on the scalp. The essential lesion was a small papule, varying in size from that of a pinhead to that of a millet-seed; some of the lesions, however, were capped each with a tiny pustule. The arrangement was either in isolation or in groups of four or five. The lesions were reddish or reddish-brown and soft to the touch. Some were capped with a scale. Comedones and telangiectasia were not present. The patient complained of an occasional slight itching. There were a few lesions on the mucous membrane of the lower lip.

Biopsy showed lupus miliaris disseminatus. Clinical examination of the heart and lungs yielded a negative result. Roentgen examination of the chest showed no abnormalities in the heart and lungs.

VARICOSE ULCER TREATED WITH INJECTIONS OF SODIUM SALICYLATE. Presented by DR. COMBES.

D. N., from Bellevue Hospital, had had varicose veins for about twenty years. Fifteen years before presentation a varix over the right ankle had ruptured and after the rupture an ulcer had developed. The ulcer had been excised, and the wound had slowly healed. Four years before the patient had first been seen by Dr. Combes, another ulcer had appeared at the same site, and this had remained open. At Dr. Combes' first visit (Nov. 8, 1928) the patient showed an ovoid, deep, punched-out ulcer the size of a dollar over the inner malleolus of the right leg, surrounded by a palm-sized patch of eczema. On the outer side of the left calf was a small superficial varix almost ready to rupture. Many large tortuous varices were present on the legs and thighs. On Nov. 8, 1928, 5 cc. of 20 per cent sodium salicylate was injected into one of the varicose veins, and a tight elastic bandage applied. Two days later the vein was found to be flat and obliterated. After this, an injection was made every week, at first of a 20 per cent and later of a 30 per cent solution. The injection was made with the patient standing and no tourniquet was used. At the same time, Lassar's resorcinol paste was applied locally to the ulcer, and the legs were supported by an elastic bandage. On December 27, the ulcer had completely healed. Since then injections had been continued so as to obliterate all the superficial varices on the legs and thighs. Altogether, twenty-two injections had been given.

DISCUSSION

DR. SPIEGEL: I have had some fine results with injections in the treatment of varicose veins, using a 30 per cent solution of sodium thiosulphate, and having the patient stand, as Dr. Combes did. Dr. Caro of our clinic has had considerable experience with this treatment.

DR. CARO: We have been having the patient stand up and have not been using the tourniquet. We insert the needle, with the point directed upward; we allow 1 cc. of blood to flow into the syringe and we inject a 30 per cent sodium salicylate solution into the vein. We do not withdraw the blood from the vein, but inject the solution into the distended vein. We have not had any experience with dextrose, but, according to the papers written on the subject, the use of dextrose is not as certain in its results.

DR. ABRAMOWITZ: The result obtained is excellent. I would recommend it in the treatment for varicose veins and ulcers, but not in patients with varicose veins due to pelvic obstruction or in patients with heart trouble. Diabetes and periphlebitis are also contraindications. At the Post-Graduate Clinic, Dr. Felden has been carrying out the treatment. He prefers a 20 per cent solution of sodium chloride. As far as technic is concerned there are bound to be different methods. Some have the patient standing, others sitting or lying down. I think the most important thing is to determine the patency of the veins, and make sure that there is no contraindication to the treatment.

DR. ROSTENBERG: After inserting a needle, I let the blood in that part of the vein run out and then inject the solution. I have seen the injection made with milk, dextrose, etc. The results were excellent. After from two to three injections, the vein becomes obliterated; the patient has no pain.

DR. CANNON: I have been thrombosing varicose veins with sodium salicylate since the early part of 1925, and to date have treated about 300 people with a total of several thousand injections. I have had excellent results. I strip the larger veins of blood before injecting the sodium salicylate, believing that one has then a more direct contact of the drug with the vein wall. Bandaging the legs with Unna's zinc gelatin paste is important, especially when there is an ulcer. I believe that such bandaging lessens the possibility of emboli, gives support to the circulation and, by its uniform pressure, relieves the pain and soreness after the injections. I have used various irritants to thrombose veins and prefer sodium salicylate because of the thoroughness with which it does the work and the rarity with which it is followed by unpleasant symptoms and the infrequence of sloughing at the site of the injection. Sugar solutions are much less painful, but one does not get anything like the same degree of thrombosis from their use.

DR. SAUNDERS: At the French Hospital, I have treated four cases of varicose ulcer and one of varicose eczema by the technic described by Dr. Caro, with good results.

DR. BECHET: The method seems exceedingly promising; there have been, however, a few deaths from pulmonary embolism. It would be a good plan to have members of the section report whatever bad results they encounter, thereby establishing whether or not there is absolute safety.

DR. COMBES: As regards the bad results, such as pulmonary embolism, I do not believe there have been any cases reported in the literature, of bad results following injections of sodium salicylate. The deaths followed injections of dextrose.

ACTINOMYCOSIS. Presented by DR. HOPKINS.

C. P. G., white, a schoolboy, born in the United States, had had a right lower premolar tooth extracted in April, 1928. One month later, swelling had appeared on the chin and had gradually increase without causing pain. The abscess opened spontaneously, after which healing set in, leaving only slight swelling. In November, 1928, a similar tumor on the left side opened and drained. A roentgenogram showed new bone formation at the lower border of each mandible, probably the result of periosteitis.

On presentation there was a stony hard, slightly tender mass under the chin with little draining. Microscopic examination of the discharge from the sinus revealed a few sulphur granules containing a streptothrix fungus without definite clubs.

MONGOLIAN SPOTS. Presented by DR. ANDREWS.

E. B., colored, aged 4½, born in the United States, a patient from the Vanderbilt Clinic, had bluish-brown pigmented areas of irregular outline in the sacrolumbar region. These had been present since birth and were more marked originally than they were when presented.

MOLLUSCUM CONTAGIOSUM (EXTENSIVE). Presented by DR. FEIT.

A patient from the New York Skin and Cancer Hospital said that she had first noticed an eruption on the front part of her body two weeks after having taken a Turkish bath and that it had been present for seven weeks. It had started on the lower part of the abdomen, the lesions gradually increasing in number and involving the larger part of the body. The lesions consisted of small umbilicated nodules with an erythematous face. In the beginning, the eruption had been attended with much itching. The patient had not taken drugs. Molluscum bodies could be expressed. The mucous membranes were free. The Wassermann reaction was reported negative. Most of the tumors were removed by desiccation.

ARSPHENAMINE DERMATITIS. Presented by DR. FEIT.

E. H., colored, aged 45, born in the United States, an elevator operator, had had a generalized eruption, located especially on the extremities, for three months. In 1923, the patient had had a similar condition confined to the elbows, hands and popliteal spaces.

The skin was extremely thick and infiltrated, and showed marked desquamation. The hands were swollen, edematous, and marked with numerous cracks and fissures. The feet were dry. A slight edema was present around the ankles. There were numerous small intradermal vesicles, especially on the chest and back. Scratch marks were not visible, although the patient complained of intense itching. The patient had not had antisyphilitic treatment since 1924.

The blood chemistry on Feb. 7, 1929 showed: sodium chloride, 471 mg.; sugar, 101.8 mg.; bile, 0; urea nitrogen, 10.9 mg., and uric acid, 5.75 mg. The examination for arsenic in the urine on January 31 showed 8.52 mg. per hundred grams of dry specimen. The Wassermann test, February 17 showed both antigens 3 plus; the Kahn test, 3 plus.

GENERALIZED ERYTHRODERMA. Presented by DR. CANNON.

L. F., a white man, aged 67, German, working in a restaurant, was admitted to the City Hospital on Jan. 21, 1929, complaining of incontinence of urine and a generalized rash. He gave a history of having slept in a mission for six months prior to coming to the hospital, at which time he contracted pediculosis. Itching had persisted. He was not definite about the changes and color of the skin, but he believed they had begun about the same time that the itching and appeared.

Examination of the patient showed a fairly well developed and well nourished man, with a generalized yellowish-brown pigmentation of the skin. The skin was dry and thickened and covered by many slightly elevated papules varying in size from that of a pinhead to that of a pea; most of them had been scratched to the point of leaving excoriated tops. He also had linear scratched marks on the legs and shoulders. The inguinal glands were each the size of a pigeon's egg and firm. The urine showed a faint trace of albumin, but otherwise was negative. The Wassermann reaction was negative.

DERMATITIS MEDICAMENTOSA (PHENOLPHTHALEIN). Presented by DR. COMBES.

D. W., a negress, aged 38, gave a history of the onset six months previous to presentation of an erythematous patch in the midline of her neck and a blister on her upper lip. There was mild pruritus. The inflammatory symptoms gradually disappeared leaving pigmentation.

On examination, she presented a definitely marginated, uniformly pigmented, nonelevated, noninflammatory, oval lesion in the anterior midline of her neck. The lesion was about 4 by 8 cm. in diameter. A similar circular patch about 2 cm. in diameter was present on her upper lip directly below the nose.

Although she had for years taken laxatives containing phenolphthalein, she had taken them more frequently and had varied the preparations during the six months prior to presentation. The Wassermann reaction was 4 plus.

LUPUS VULGARIS. Presented by DR. CANNON.

W. C., a colored man, aged 23, born in New York, a switchboard operator, was first seen in the City Hospital in 1922; at that time on the right cheek he had extensive lesions that had been present and untreated for about four years. Under general anesthesia, the ulcerated area was thoroughly curetted and cauterized with trichloracetic acid and he was discharged cured several months later. He remained well for about three years, and then new lesions appeared around the margin of the old scar. He returned to the hospital, and again the lesions were curetted and cauterized and healed. A year and a half later, he returned. A piece of skin was taken from the chest and grafted over the scar, with successful results. He was re-admitted on Feb. 20, 1929, because of new lesions on the tip of the nose and on the right cheek. The patient felt well and had suffered no loss of weight.

Examination showed the tip of the nose to be covered with a quarter-sized, elevated, yellowish, crusted sore, which extended down to the nasal septum. Involving the right corner of the mouth and outer canthus of the right eye were flat, scaly, pigmented lesions. The left cheek was covered with a palm-sized area of apparently normal skin around the margin of which was a depressed white scar. The upper and lower lips were covered with dry, scaly, pinkish-white, atrophic skin.

BROOKLYN DERMATOLOGICAL SOCIETY

Meeting, March 18, 1929

W. H. Best, M.D., *Presiding*

ACTINOMYCOSIS? Presented by DR. WALZER.

J. L., a man, aged 40, married, a salesman, presented a condition which had begun eight months previous to presentation, with a scratch on the chin following shaving, situated about 1 inch below the jaw. It soon became nodular and failed to heal. About one month later, the swelling enlarged, involving the entire right side of the face. After local applications were applied, the mass became smaller, localizing itself near the angle of the jaw. It was incised, but never completely healed. At various institutions he received twenty injections of "vaccine" into the arms and buttocks and roentgen therapy. After the treatment with vaccine, the swelling had apparently diminished, but enlarged again a few weeks later. An elongated, transverse, elevated mass, about 2 inches in length by ½ inch in width, was present under the chin, near the junction of the undersurface of the jaw and neck. There were numerous points of purulent exudation. Surrounding the entire mass, there was slight erythema with alopecia. He had a number of gold crowns; otherwise, the teeth were in fairly good condition.

DISCUSSION

DR. WALZER: The first possibility to be considered is pyoderma; the second possibility, actinomycosis, and the third, scrofuloderma. I think that we can rule out scrofuloderma, as there is no glandular involvement; it is purely an intradermal lesion. The question rests, therefore, between actinomycosis and

pyoderma. I have never seen a case of simple infection which would give a lesion of that kind. Actinomycosis, to my mind, would be a good diagnosis, if we could find the granules, but I understand from the patient that they have been looked for in other institutions as well as here and none has been found. He has been getting large doses of iodide of potash and while there has been some improvement, there is not enough to help in the diagnosis. A number of cases have been described in the literature in which there were lesions which resembled those of actinomycosis; however, *Actinomyces* was not found.

CARCINOMA AND TUBERCULOSIS OF THE TONGUE IN A SYPHILITIC PATIENT. Presented by DR. FRANK.

D. O., a man, aged 52, gave a history of tuberculosis in his family. He had a chancre for which he was treated thirty years previously. Ten years before presentation, he noticed swellings on both the upper and the lower lip. They were red and exuded a mucopurulent discharge. Seven months previous to presentation, he noticed a few areas of infiltration on the side of the tongue. At that time, he also developed a cough. The condition on the tongue spread rapidly. The patient presented ulcerations of the side and tip of the tongue. The lesions on the tip were small, circular, shallow, discrete and granulating, while those on the side of the tongue were infiltrated, hard and sharply outlined. The floor exuded a mucopurulent discharge, while the borders showed exuberant cauliflower-like tissue. The chemical analysis of the blood and urinalysis gave negative results. A roentgenogram of the chest showed apical tuberculosis.

DISCUSSION

DR. BEST: Do you think that the lesions on the tongue are gummas which have undergone malignant degeneration?

DR. CHARGIN: It is my impression that we are dealing with an epithelioma developed on top of a syphilitic manifestation of the tongue. This is certainly true of the tumor mass on the margin of the tongue. I regard the small superficial ulcerations on the surface of the tongue as traumatic in nature, and do not think that they are tuberculous. As regards therapy, I feel that this patient should receive the benefit of intensive antisyphilitic therapy for a very short time. This would serve to control such active syphilis as may be present, and also assist in the diagnosis. If there is little or no therapeutic response, immediate operation is indicated as offering the only hope in this case.

DR. WALZER: The lesions are too flat and entirely too numerous for the tertiary stage of syphilis. They are extremely tender and too raw looking. It certainly is not multiple gummas. The multiplicity, the lack of depth and the scattered white points would favor tuberculosis with a superimposed carcinoma.

LUPUS VULGARIS AND CARCINOMA. Presented by Dr. Gauvain.

D. S., a married woman, aged 53, born in Russia, appeared at the Long Island College Hospital with a lesion on the face which had first appeared when she was 2 years old, as a small swelling on the left cheek near the angle of the mouth. She was treated in Europe with ointments, and the lesion disappeared, leaving a scar. Every two or three years after that time she had had recurrences of the same condition which healed after treatment, always leaving scars. About fourteen years before presentation the entire area had been treated by the roentgen ray, and there remained some telangiectasia from this treatment. At the time of presentation, there was an erythematous lesion on the left cheek extending up to the eyelids, which caused an ectropion of the lower lid. Within this area were many small apple jelly-like nodules, and there was considerable scaling. The cheek showed a great deal of fibrous scarring, and within this, extending from the angle of the mouth, was a large verrucous area about 2 inches in diameter, raised well above the skin and having a firm cartilaginous border. This complication had been present for only about eight weeks.

DISCUSSION

DR. BEST: I suggest surgical diathermy for the removal of the cauliflower-like growth. You can then electrodesiccate the base. Why is the roentgen ray or radium contraindicated?

DR. GRAHAM: This epithelioma has developed on a roentgen dermatitis. The tissues around it are devitalized from previous roentgen therapy. Radium or roentgen therapy on top of that will not allow healing, provided the dose given is large enough to be of any value. If radium is used, it will simply cause a radium dermatitis without any tendency to heal.

DR. GAUVAIN: I was interested particularly in the opinions as to what was the method of election for removing this carcinoma. My intention was to remove it by electrodesiccation without any subsequent irradiation to the local area.

IDIOPATHIC MULTIPLE HEMORRHAGIC SARCOMA. Presented by Dr. Frank.

G. C., a man, married, a salesman, had an attack of redness and swelling of the left foot eleven years prior to presentation, which was diagnosed as erysipelas. Four years previously, he had an abscess of the foot, which was incised and drained. This condition lasted for four weeks. A year later, he noticed redness and swelling of the left foot. The pain was intense, though no temperature was present. This condition lasted for about five weeks. Two years before presentation, red, hemorrhagic areas were noticed, first on the large toe, then spreading across the entire left foot. Eight months before presentation the patient noticed a thickening on the plantar surface of the left foot which made walking difficult. Increased swelling of the foot followed. On the foot there were sharply outlined, infiltrated, hemorrhagic areas made up of dark purple, firm nodules, which were discrete and grouped. The leg was edematous, hard and bluish. Urinalysis, Wassermann test of the blood and blood count gave negative results.

DISCUSSION

DR. WALZER: I saw this man about two months ago and at that time the lesions were more pronounced. Injections of arsenic and roentgen therapy were suggested. He told me tonight that he had received drops and some sort of light treatment.

DR. CHARGIN: I agree with the diagnosis. Idiopathic hemorrhagic sarcoma is not regarded as a true sarcoma, and biopsy usually leads to no serious consequences. From the therapeutic standpoint, arsenic by hypodermic injection and roentgen exposures are indicated. Many cases clear up under this treatment and remain well for long periods, although the disease eventually recurs.

PARAPSORIASIS. Presented by DR. WALZER.

E. L., a school boy, aged 16, born in the United States, presented a rash on the body of two years' duration. His past history was negative. He presented tiny lichenoid papules on the penis and extremities. These lesions were discrete and arranged in groups. There were erythematous lesions, the size of a pea, slightly elevated, covered with a thin scale, which on scratching did not give the punctate bleeding of psoriasis. These were especially noted on the trunk. On the trunk and the upper extremities were pigmented areas, the size of a pea, probably the remains of past lesions. The mouth showed no lesions, though the posterior part of the gums showed some suggestion of white points. The palms were clear. There were no evidences of scratching.

DISCUSSION

DR. BEST: I agree with the diagnosis. The papular lesions are not typical lesions of lichen planus and some of the areas show fine furfuraceous scales.

DR. GAUVAIN: I agree with the diagnosis of parapsoriasis. Some lesions certainly look like lichen planus. The symptom complex, however, does not fit into that disease. We did find two lesions where we removed the scales and found punctate bleeding points. In spite of that, I do not think that it is psoriasis.

RECURRENT LYMPHANGITIS. Presented by Dr. Best.

H. G., a woman, aged 30, married, born in the United States, presented a condition that dated back four years, when she experienced a sudden pulsating sensation in the left cheek. The following morning, she noticed a hard, tender, red swelling in that cheek. This lasted for four days and gradually disappeared. Associated with this, there was excessive lacrimation and a marked conjunctivitis. Since then she had six similar attacks. Each left her with a waxy, edematous condition of the area affected.

DISCUSSION

DR. CHARGIN: This patient is suffering from the so-called habitual erysipelas. Each succeeding attack leaves its remnant of blocked lymphatic channels, which results in this solid edema. From the therapeutic standpoint, roentgen therapy had been suggested to reduce the infiltration and vaccines to prevent recurrences of the erysipelas.

DR. WALZER: The condition is not erysipelas. It is a specific type of lymphatic infection and obstruction. The only thing it has in common with erysipelas is that during the acute stage it resembles erysipelas. Erysipelas is a contagious disease, due to a specific organism and if it does recur, the first attack completely disappears before the second occurs. This condition may be due to many different organisms, and the site of the lesion never returns to normal. Every successive attack leaves the site larger than previously. It is, in other words, in mechanism similar to elephantiasis rather than erysipelas.

DR. WALZER: These are really cases of recurrent attacks of lymphangitis, directly under the skin which cause obstruction of the lymphatics and, hence, solid edema.

CHICAGO DERMATOLOGICAL SOCIETY

Regular Meeting, March 20, 1929

FRANCIS E. SENEAR, M.D., *President, in the Chair*

A CASE FOR DIAGNOSIS. Presented by DR. HEDGE.

Mrs. K., aged 27, white, a housewife, for the past seven years had a generalized eczema, which appeared without apparent cause. She had seen Dr. Fox, Dr. Fordyce and Dr. Beers of New York and Brooklyn, Dr. O'Leary at Rochester, Dr. Mount of Albany and many others. In spite of local or internal therapy, the trouble persisted. The blood count showed 4,600,000 red cells and 8,620 white cells; the differential count was normal. The Wassermann reaction was negative. The blood pressure was 102 systolic and 60 diastolic. The urine was normal. The patient had had considerable quartz lamp and roentgen therapy; she had been given calcium internally, all sorts of applications locally, sodium hyposulphite intravenously, thyroid extract, injections of foreign protein and roentgen irradiation to the dorsal ganglions. She was presented for suggestions as to possible diagnosis and for treatment. Following her pregnancies she had puerperal fever, during which the irritation subsided.

DISCUSSION

DR. OLIVER: I agree with Dr. Harry Foerster, who said that he thought the patient was subject to polytherapy rather than to too little therapy. It is

the type of case that almost nothing seems to benefit. I believe that she should be tested with more food proteins.

DR. STILLIANS: Dr. Hedge told me that when Dr. O'Leary saw this patient he put her to bed, bandaged the lesions for several weeks, and the condition cleared up. I think that perhaps that was what she needed for the low blood pressure.

DR. BECKER: The patient said that she first had pruritus and that the lesions appeared only after scratching. The buccal mucosa is not hyperpigmented, and the hyperpigmentation may all be due to ultraviolet irradiation or irritation from scratching. I am interested to hear that she had a low blood pressure, and I think that she probably has a low metabolic rate as well. The condition seems to be prurigo or neurodermatitis.

DR. H. R. FOERSTER: The hyperpigmentation and lichenification might be considered as due to persistent scratching.

DR. MCEWEN: I believe that this is a case of food sensitization, and that if the patient was put through the sensitization tests for foods a group would be found to which she is sensitive.

DR. PARKHURST: In two similar cases I investigated thoroughly for food sensitization, and also for internal glandular abnormalities, with no result whatever.

DR. HEDGE: I am much indebted for the suggestions made, particularly for the one regarding low blood pressure and low metabolic rate, and for Dr. Becker's suggestion of glandular therapy. That is about the only thing we have not tried. I will run through a series of protein sensitization tests, and if anything interesting develops I will report it later.

NOTE: The basal metabolic rate has since been determined, and found to be minus 10 per cent.

A CASE FOR DIAGNOSIS (IDIOPATHIC ATROPHY). Presented by DR. SENEAR and DR. WIEN.

C. S., a housewife, aged 31, first noted a mild pruritus in the left axilla in June, 1928. Soon afterward, a depression was noted in the pruritic area; the depression and pruritus had increased progressively to their state at the time of presentation. For the past five months there had been an associated feeling of numbness in the left arm and leg. There were no other subjective sensations. She had received no treatment locally. Itching was almost continuous and had been associated with a crawling sensation in the area since June, 1928.

The left midaxillary region, at the lower rib border, was the site of a linear depression that corresponded to the pressure area of the upper edge of the corset. The area measured 2 by 10 cm., and the central portion was occupied by five or six atrophic spots, varying in size from that of a pea to that of a bean. The subcutaneous tissue was entirely absent in the area, and the underlying ribs were readily felt on palpation. Examination of the chest was negative, as were the Wassermann and the Kahn tests of the blood.

DISCUSSION

DR. FINNERUD: I thought that this condition might be a pressure deformity, with pressure atrophy of the cutaneous and subcutaneous portions. I could not account for the punctate atrophic scars, unless they are the relics of some preceding disorder, such as shingles.

DR. HEDGE: I was interested in the fact that the scar tissue could be moved up with perfect freedom but could not be pulled down. It must be attached to some bony growth, and that brought to mind the possibility of some herpes or other disease that might cause the general destruction.

DR. SENEAR: There is a distinct atrophy involving the subcutaneous tissue. We could not account for the superficial scars Dr. Finnerud spoke of, but it is

possible to push the fingers into the side and feel the ribs plainly, while on the other side there is plenty of fatty tissue over the ribs. We regard the condition as a form of idiopathic atrophy.

A Case for Diagnosis. Presented by Dr. Oliver.

A boy, aged 17, first seen on February 1, had a maculopapular eruption on the anterior abdominal surface, the anterior surface of the chest, the flexor surface of the forearms and, to a slight extent, on the back and legs.

Most of the lesions were about half the size of a split pea. On some there was a slight amount of scaling and some tended to become vesicular. The color was yellowish brown. Some of the lesions had become excoriated.

The condition had become much worse in the last month. The boy's general health was good; there was no adenopathy. There was little itching, and the Wassermann reaction was negative.

DISCUSSION

Dr. Wile: If our diagnostic criteria are not too rigid, I should like to make an unusual case of dermatitis herpetiformis out of this. The lesions are polymorphous and considerably pigmented. There is no grouping, but there is itching when the blisters appear, and I think that with a little latitude for unusual cases it might fall into that group.

Dr. Ormsby: My first impression of the case was that it was pityriasis lichenoides chronica, but vesicles are not usually present in that disorder, and I also thought that there was a resemblance to a syphiloderm. I believe with Dr. Oliver that it is a distinct entity, which he will probably be able to demonstrate.

Dr. Nomland: From the biopsy which I ran through for Dr. Oliver I think that there is no doubt that there are deep-seated vesicles present in the piece removed.

Dr. Oliver: Dr. Senear and I have been much interested in this case because of a similar case of his that we saw about the same time. When we first saw both cases we were sure that they were cases of maculopapular syphilis. In this boy's case and in Dr. Senear's case two Wassermann examinations gave negative results. These cases resemble a maculopapular syphilis, a pityriasis lichenoides chronica and, in some ways, a varicella.

Dr. A. M. H. Gray, in the January, 1929, issue of the *British Journal of Dermatology*, reports one case and tells of another he had previously shown.

These cases of ours are the same condition that has been described by him, Almkvist and several others under the name of pityriasis lichenoides et varioliformis acuta. The original case was described by Mucha in 1916.

It is a papular eruption which resembles a papular syphilid or a pityriasis lichenoides chronica. Sometimes it itches, sometimes it does not. Among the papules may be seen inflammatory papules, occasionally pustules and vesicles, which leave varioliform scarring when the crust drops off. The disease runs an acute course, generally subsiding in six months, with no tendency to recur.

Dr. Wile: Do you regard the case as parapsoriasis?

Dr. Oliver: No, it resembles a pityriasis lichenoides chronica very much in its clinical aspects, but runs a much shorter course. Both of Dr. Gray's cases ran an acute course, one about six months, and then the condition cleared up entirely.

Dr. Wile: I think that it is too bad to confuse a picture that is perfectly plain with some other condition. This case is either parapsoriasis or it has nothing to do with it. I wonder whether Dr. Gray has not been describing a condition under a name that has nothing to do with it.

Dr. Senear: I think that a striking point this case brings out is that some of these cases resemble a secondary syphilid so closely and some the pityriasis lichenoides chronica of Juliusberg. My case was seen first and we regarded it

unquestionably as one of secondary syphilis, but we eliminated that diagnosis after two negative Wassermann reactions and because the patient had no history or signs of that infection. When I saw this case with Dr. Oliver my first thought was that it was pityriasis lichenoides chronica, but the vesicular element followed by crusting did not fit into that picture.

NOTE: The condition in this case cleared up entirely in four months.

A CASE FOR DIAGNOSIS (PRURIGO NODULARIS). Presented by DR. ORMSBY.

A woman, aged 44, had had an intensely itching disorder for four years, beginning at the menopause. The itching had been worse at night and interfered with sleep. She said that "lumps" like mosquito bites appeared and usually remained indefinitely, although some did disappear.

The eruption consisted of moderately elevated, infiltrated, discrete nodules, the size of a pea. Some were pale red, others colorless. They were situated chiefly on the forearms and thighs and to a lesser degree on the arms and legs. Some infiltration was present in the skin between the nodules, and much excoriation occurred on the trunk. The blood pressure was 130 systolic and 90 diastolic. The differential white cell count showed: polymorphonuclear neutrophils, 63 per cent; large lymphocytes, 5 per cent; small lymphocytes, 25 per cent; eosinophils, 6 per cent, and transitionals, 1 per cent. The urine was normal.

The principal histologic change was in the upper corium where a rather dense round cell infiltration was present. This occurred about dilated blood vessels and in the region of hair follicles and coil glands. The epidermis showed a slight acanthosis and slight hyperkeratosis, with a moderate increase in pigment in the basal area (Dr. Finnerud).

Treatment over a period of eight months had had practically no effect on the disorder. Arsenic and calcium lactate internally and calcium chloride intravenously had been employed with various topical applications.

DISCUSSION

DR. WILE: I believe that this is a case of nodular prurigo. It seemed to have all of the characteristics one usually associates with that condition. I think that sometimes it is hard to draw a line between when a persistent urticaria ceases to be that and deserves the name of prurigo. The lesions of nodular prurigo never look much like true urticaria to me. They are usually much different in size and feel much harder, almost a fibrosis; this case, I think, stands out well as an example of this condition.

One thing I wish to mention, substantiating the statement I made some time ago regarding the microscopic examination of subpapillary lesions, is that I do not think that lichen planus can always be diagnosed by microscopic examination. In this case one could with little imagination take the microscopic slide and picture to himself a lichen planus. I think that we should be guarded in establishing a diagnosis of lichen planus from microscopic sections, for many other conditions look much like it.

DR. LIEBERTHAL: I agree with the remarks of Dr. Wile. The similarity in the microscopic appearance of lichen planus hypertrophicus and prurigo nodularis is quite marked.

DR. FINNERUD: We went over the sections carefully and figured out that the picture could correspond well with either that of prurigo nodularis or of lichen planus hypertrophicus. It has practically all the characteristics of both disorders.

DR. SENEAR: I was interested in this case because of a group that we discussed several years ago—the neurotic excoriation group. I did not feel that this case fell into that classification, but in the discussion of those cases it was usually brought out that there was a preliminary lesion which gave rise to the neurotic excoriation. I had not thought of this case as one of neurodermatitis, and agree with the diagnosis of prurigo, but I noticed that many of the lesions

were similar to acne urticata. I thought that it might possibly be that disorder, although clinically it corresponded to prurigo nodularis.

DR. BECKER: We have been studying patients who have primary pruritus, with or without secondary manifestations, such as neurodermatitis, and find that practically all of them fall into the group of patients with suprarenal insufficiency, with low blood pressure and low basal metabolic rate. We have been able to improve their general condition and also the dermatitis by oral administration of cortical suprarenal substance.

DR. ORMSBY: The discussion agrees with my view of the case. The point is that there is a tendency recently to group these cases with those of neurodermatitis, or lichen simplex chronica, from which they distinctly differ. It corresponds with prurigo nodularis as described by Hyde. I have seen a number of cases and they all have the same history. Marked itching occurs in both disorders, but the lesions are different. This patient said that there had been itching before the lesions appeared, but I have kept watch carefully and invariably the lesions precede the itching.

A CASE FOR DIAGNOSIS. Presented by DR. OLIVER.

A boy, aged 9, complained of an eruption of six years' duration. The lesions were papules, some acuminate, some flat-topped, for the most part the size of a pinhead, arranged in definite groups the size of the palm over the scapulae, both upper arms, the front of the abdomen, the sides of the back and the popliteal spaces. The itching was marked.

DISCUSSION

DR. H. R. FOERSTER: I consider this condition as possibly a case of allergic dermatitis. A papular type of Duhring's disease should also be considered, principally because of the duration of the eruption, its distribution and the history of lesions occurring in crops.

DR. WHITE: I agree with the diagnosis of dermatitis herpetiformis.

DR. FINNERUD: I tried to make dermatitis herpetiformis out of the condition but had some difficulty and came to the conclusion that it must be allergic dermatitis, so-called, or perhaps an unusual manifestation of prurigomitis, despite its distribution.

DR. LIEBERTHAL: For several months we have had a case under observation that is an absolute duplicate of this. The patient, a boy, aged 10, was at the Mayo Clinic and our dermatologic friends there inclined to the diagnosis of dermatitis herpetiformis.

I agree to this diagnosis in both instances.

DR. SENEAR: I have been much interested in this case because recently we had a boy about 5 at the dispensary whose eruption was of only two weeks' duration. If we take away the signs of chronicity in this case, it is a duplicate. The case is not as multiform in type as we expect in dermatitis herpetiformis, and we thought of a lichen urticatus with grouping, which would be along Dr. Foerster's suggestion. I think that the present case is dermatitis herpetiformis.

A CASE FOR DIAGNOSIS (LICHEN PLANUS? LICHENOID ARSPHENAMINE ERUPTION?). Presented by DR. NOMLAND (by invitation).

A woman, aged 35, had a generalized maculopapular eruption which involved the entire body, including the face and extremities. She said that she began treatment for syphilis at the Central Free Dispensary, Rush Medical College, in April, 1928, where she received two courses of soluble bismuth, fifteen injections each. Between these courses she received six intravenous injections of neoarsphenamine, with no ill results. In December, 1928, a second course of neoarsphenamine was given, and after the first injection she developed an itching

eruption of the skin, which was aggravated with each succeeding injection. This was thought to be pityriasis rosea, or seborrheic dermatitis. In spite of this eruption a course of six injections was given, without great aggravation or amelioration of the rash. The itching was moderate.

When presented, the eruption consisted of brownish-red, oval, lichenified, scaling maculopapules, varying from 0.5 to 1.5 cm in diameter. The long axis of the lesions followed the lines of cleavage on the body. In some areas where lesions had formerly been there was a purplish-brown stain, which seemed to be slightly atrophic. In the mouth a few, indefinite, whitish areas were observed.

Biopsy from a lesion on the back showed a normal stratum corneum and stratum granulosum. There was slight acanthosis. The papillary and subpapillary layers of the dermis were the sites of a dense infiltrate of round cells, which had invaded the basal layer of the epidermis, causing colliquative degeneration. The infiltrate was quite sharply limited at its lower border and decreased gradually to either side. In the deeper cutis, it was definitely perivascular. It was also present about the adnexa. The capillaries of the subpapillary layer were in some places definitely and markedly dilated. Staining with Pappenheim's and with polychrome methylene-blue showed that plasma and mast cells were rare, and that the cells were practically all lymphocytes, with a few fibroblasts.

DISCUSSION

DR. MITCHELL: I think that perhaps this is a case of lichen planus due to arsphenamine.

DR. BECKER: I believe that it is a case of lichenoid dermatitis due to arsphenamine. Many of the lesions on the back are spinulous. We recently had a spinulous eruption following the administration of gold sodium thiosulphate.

DR. WHITE: The unusual thing to me was the presence of the spines; I was unable to evaluate their significance.

DR. NOMLAND: I made my diagnosis on the white patches in the mouth, and because of the suggestive pathologic changes which are fairly typical of lichen planus.

EPITHELIOMATOSIS: MULTIPLE, SUPERFICIAL. Presented by DR. NOMLAND (by invitation).

A man, aged 71, was first seen in 1924, because of an epithelioma of the outer canthus of the right eye. The lesion had been treated elsewhere with roentgen therapy but had recurred. Surgical excision followed by skin grafting was done at this time. In 1926, there was a recurrence of the growth, which was then treated with the roentgen rays, with moderate success. He returned with another recurrence in the summer of 1928.

In 1924, he complained also of a chronic, scaling eruption on the sternum, back and other areas of the body which he said had been present for forty years, clearing up periodically on the application of ointments. A general practitioner had made a diagnosis of psoriasis, but Dr. Montgomery made a diagnosis of multiple superficial epitheliomatosis. There was no further note of this condition until the summer of 1928, when the patient said that the lesions present in 1924 had grown larger and that new ones had appeared. They had not responded to ointments as they formerly did. One of the lesions on the forearm which began as a scaling lesion had become ulcerated, and an elevated ulcerating lesion had appeared in the left groin and grown rapidly in the past year. He did not know whether or not this lesion began as a scaling patch.

Examination revealed a rather poorly nourished man. The outer canthus of the right eye was the site of an epithelioma which involved the conjunctiva as well as a portion of a plastic flap. On the sternum and interscapular region were several dozen round, scaling, slightly reddened lesions, averaging the size of a split pea, which were almost identical in appearance with a dry, scaling, seborrheic

dermatitis. The larger lesions were slightly indurated, and minute pearly nodules and threadlike lines could be made out at the peripheral borders. Similar scaling lesions occurred on the arms and abdomen, in the pubic region and elsewhere, but were not so numerous. On the forearm was a single lesion, presenting a cleancut ulcer 1 cm. in diameter, which was not greatly indurated but showed areas of a scaling halo. In the left groin was a hard, elevated, ulcerating lesion, 2 cm. in diameter. The border was pearl-like and at its upper margin showed a peculiar brown pigmentation. A small, unpigmented lesion was present in the region of the coccyx. No enlarged glands could be palpated in the inguinal region or on rectal examination. There were also many greasy, scaling, seborrheic keratomas in the seborrheic areas.

Biopsies were taken from three different types of lesions present. Biopsy 1, from the superficial ulcerating lesion of the left forearm, showed deeply infiltrating strands of dark-staining epithelioma cells invading the cutis. At the border they could be seen to take their origin from the basal cell layer. This origin was different from that seen in the ordinary basal cell epithelioma in that a larger number of contiguous basal cells gave rise to the new growth. The cells were different than the small, darkly staining cell of the ordinary basal cell epithelioma. They were larger and less constant as to type, and showed dyskeratosis. Rather well developed pearls were present at the border of the ulcer, and beneath the ulcerated area strands of cells formed a large, meshed reticulum, giving rise to the formation of pseudo-acini.

Biopsy 2, from the elevated, cartilaginous lesion in the groin, showed rather large islands of dark-staining cells of the basal cell type arising from the basal cells of the epidermis. The origin was more typical, in that only a relatively few contiguous cells took part. The cells were uniform in type. There were areas, particularly at the border, which contained many pigment-bearing cells, and there were also several round spaces which contained a large amount of pigment, apparently lying free. Some of the cell islands showed cystic keratinization at the center, but there was no pearl formation.

Biopsy 3, from a typical scaling lesion on the upper arm, showed basal cell epithelioma of the superficial type.

A man with superficial scaling lesions of many years' duration, and a few lesions of a different type of relatively short duration, was shown by biopsy to have: (1) numerous superficial basal cell epitheliomas; (2) one ulcerating lesion in which the microscopic picture was midway between the basal and prickle cell epithelioma, and could be classified with the metatypical, or basosquamous, epitheliomas, and (3) an atypical basal cell epithelioma with much melanin pigment in it.

DISCUSSION

DR. H. R. FOERSTER: This is an interesting case and well worth seeing.

DR. WHITE: I should like to know whether the clinical diagnosis was made before the biopsy was taken.

DR. FINNERUD: Dr. Nomland and I first saw this patient together at my clinic, and one of the patches impressed us clinically as though there should be a Bowen's type of histology, and we were surprised not to find it. Some of the lesions, however, we felt definitely should be basal cell growths, and this they proved to be.

DR. NOMLAND: The lesion Dr. Finnerud mentioned is the one that showed the metatypical squamous cell epithelioma. The others are all pure basal cell growths.

DR. ORMSBY: I saw the patient's record that was made by Dr. Montgomery in 1924. The growths all look like basal cell epitheliomas. The striking thing about the principal lesion was that it metastasized, but it was benign and the patient went on with the growth for several years. The appearance of the lesion is that of basal cell epithelioma, and I think that no one could distinguish it without a biopsy.

LICHEN PLANUS. Presented by DR. NOMLAND (by invitation).

A man, aged 42, was first seen at the Cook County Hospital, complaining of an itching eruption of about two years' duration. It was first noticed as reddish, itching papules on the face, which soon appeared also on the body and rapidly became brown. New lesions had appeared and the old ones had become larger.

When presented, the skin was involved in a generalized eruption of pigmented lesions, varying in size from 2 or 3 mm. to 3 cm. in diameter. There was definite grouping about the sacral region, along the spine, about the neck, on the chest, abdomen, inguinal regions and along the flexor aspects of the extremities. The typical lesion was an atrophic, brown, pigmented, oval, depressed macule with a suggestion of small papules on its border. There were several whitish lesions in the mouth. In the scalp was a large, nonpigmented, atrophic, slightly irregular patch 5 by 10 cm. in its greatest dimensions. On the right forearm was a similar atrophic lesion, with a reticulated pigmentation 6 by 3 cm.

Biopsy from the border of a large atrophic lesion on the forearm showed marked increase in the stratum corneum, relative increase in the stratum granulosum and marked atrophy of the prickle cell layer, which in some places was only two or three cell rows thick. The rete pegs were absent. The papillary and subpapillary layers showed only slight remnants of a sharply marginated round cell infiltrate. There was considerable infiltrate about the horizontal running vessels of the upper cutis. There was moderate pigmentation of the basal cell layer, as well as marked increase in the chromatophores of the cutis. Acid orcein stain showed almost complete destruction of the elastic fibers in the papillary and subpapillary areas where the infiltrate was still present, and absence of the elastic tissue in those regions in which the infiltrate had almost completely disappeared. The elastic fibers of the deeper cutis were thickened, ran parallel to the surface and showed fragmentation.

DISCUSSION

DR. SENEAR: I presented this man about a year ago, I think. He had then just completed a course of injections of neoarsphenamine, the case having been mistaken for one of secondary syphilis. I showed the patient because of the extensive lichen planus in the temporal region, and with the idea that the arsphenamine might have accounted in part for the extreme pigmentation. This was one of the cases I had in mind last month at Ann Arbor when we were discussing the negative importance of distribution in lichen planus.

PARAPSORIASIS EN PLAQUE (BROCQ). Presented by DR. NOMLAND (by invitation).

A man, aged 49, in good health, had an eruption of about five years' duration. He said that a few new lesions appeared from time to time and that the old ones never completely disappeared. There was slight itching and redness, which was aggravated by worry.

Examination revealed a generalized eruption of from 150 to 200 scaling macules, which were most numerous on the arms and thighs. The lesions were oval or round, pale red, sharply outlined, furfuraceous, scaling macules, which varied in size from 0.5 to 6 cm. or more in diameter. The older lesions were present as brown stains, without atrophy. There were no lesions in the scalp or mouth. There was no history of the ingestion of drugs, such as phenolphthalein. The Wassermann reaction was negative.

Biopsy from a lesion on the forearm showed moderate parakeratosis of the stratum corneum. The rete pegs were irregularly widened and some were considerably elongated. There was moderate edema of the papillary and subpapillary layers of the cutis; moderate perivascular infiltrate was present about the capillaries of the cutis, most marked in the subpapillary region. There was also some diffuse infiltrate in this region, which consisted principally of round cells of the lymphocytic type, with a few fibroblasts. There were practically no plasma cells,

but a polychrome methylene-blue stain revealed a number of mast cells both in the perivascular infiltrate and away from the vessels in the papillary and subpapillary regions.

DISCUSSION

DR. MITCHELL: I was interested in this case from the standpoint of possible drug eruption. The patient gave a definite history of the lesions lighting up and subsiding. He feels sure that they always become red when he is constipated, and when he is constipated he always takes something. He was rather vague in his answers and I could not determine whether it was the phenolphthalein pill he was taking or something else. His susceptibility to phenolphthalein should be investigated.

DR. NOMLAND: I cross-questioned this patient about phenolphthalein when I first saw him, but apparently his usual laxative is one of the salines. He has not been tested out for phenolphthalein.

DR. H. R. FOERSTER: I concur in the diagnosis, but believe that an erythema perstans of the phenolphthalein type must be ruled out.

A CASE FOR DIAGNOSIS. Presented by DR. FINK (by invitation).

A boy, aged 14, had an eruption of six years' duration, which he thought was less marked in the winter. When presented, the trunk and thighs showed a generally distributed eruption, which consisted in reddish-brown, grouped papules, varying in size from that of a pinhead to that of a pea. Each group showed considerable brownish pigmentation surrounding or adjacent to the lesions. Relics of previous lesions were present as well defined, whitish scars of varying size. There was no history of the ingestion of drugs.

DISCUSSION

DR. WILE: I thought of two or three possibilities—a pityriasis lichenoides Juliusberg, or urticaria pigmentosa, although I could not make the lesions urticate much, and of an old, chronic psoriasis. My best guess would be a slightly unusual lichenoides chronica.

DR. MITCHELL: I thought the eruption was urticaria pigmentosa. There was definite urtication of some of the lesions when friction was applied.

DR. EUGENE LIEBERTHAL: On friction, one lesion on the elbow showed bleeding points, and I thought of psoriasis.

DR. FINNERUD: I considered this condition pityriasis lichenoides chronica. I have seen several cases, possibly some of them more typical than this, in boys of about the same age. The boy says that he is sure no one of the spots has ever gone away.

DR. FINK: I had in mind psoriasis, owing to the distribution, but in examining the section I found no resemblance whatever to psoriasis. The boy has had arsenical medication, and from the history it appears that the lesions respond markedly to arsenic. I have not had an opportunity to try this, but it puts it in the class of cases that respond to arsenic. I was particularly interested in the amount of pigmentation and the color of the area surrounding the lesions. I have talked to the patient and his father and they both agree that under arsenic the lesions clear up considerably.

COMEDONES. Presented by DR. CLEVELAND WHITE.

An American laborer, aged 37, had had acne of the face and extremities for eighteen years, which he believed had been benefited by a successful vaccination for smallpox three years before presentation. He said that various local applications had been used without benefit.

Examination showed an unusual number of comedones present on the usual acne vulgaris areas, in the axillae and on the extremities. On the cheeks and

extensor surfaces of the extremities were many follicular papules and pustules with numerous depressed scars.

Cultures from the pustules were negative for bacteria. The Wassermann reaction of the blood and urinalyses gave negative results, as did the roentgenographic examination of the chest. Biopsy was compatible with ordinary acne vulgaris.

DISCUSSION

DR. ORMSBY: I was interested to see comedones and acneform lesions in areas such as these without any outside etiologic factor. I have seen a number of them on the thighs and abdomen, but in those cases there was either an organic oil or some tarry preparation employed in the patients' occupation that caused them. This patient has lesions on parts of the body that are protected, where we seldom see them. In addition, he has scars. There is undoubtedly a process going on that does not belong to the ordinary acne group.

DR. WHITE: I should like to hear some comment on the possibility of its being in the acne varioliformis group. We considered this a case of marked comedone formation with extensive scarring.

DR. FINNERUD: The interesting thing about the case to me was that the comedo lesions were capable of producing varioliform scarring. A suitable name for this unusual condition might be acne et comedo varioliformis. Apparently the comedones as well as the acne in this case are responsible for this type of scarring.

DR. ORMSBY: Acne varioliformis is such a distinctly suppurative disorder that I do not think we could put this case in that group, notwithstanding that there are scars due to the comedones as well as to the acne. It is an interesting case.

Book Reviews

DIE TECHNIK UND ANWENDUNG DER SUBOCCIPITAL ODER ZISTERNENPUNKTION. By DR. MED. ALOIS M. MEMMESHEIMER, Privatdozent an der Klinik und Poliklinik für Hautkrankheiten der Universität Tübingen. Price, unbound, 8.50 Rm.; bound in linen, 10.50 Rm. Pp. 88, with 35 illustrations. Leipzig, Montana-Verlag A. G., 1929.

This brochure is a careful and full consideration of the whole subject of cistern puncture. The topographical anatomy, technic, dangers, precautions, advantages and results are all gone into clearly and with full detail. There are also a historical introduction, a final chapter summarizing the subject and a bibliography. It is altogether a book that is needed, and the work has been well done. The paper, the printing, the illustrations and the format of the book in general are excellent.

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AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Jay Frank Schamburg, Chairman, 1402 Spruce St., Philadelphia.
William H. Guy, Secretary, Jenkins Arcade, Pittsburgh.
Place: Detroit. Time: June 23-27, 1930.

AMERICAN DERMATOLOGICAL ASSOCIATION

Udo J. Wile, President, University Hospital, Ann Arbor, Mich.
C. Guy Lane, Secretary, 416 Marlborough St., Boston.
Place: Cleveland. Time: 1930.

BRITISH ASSOCIATION OF DERMATOLOGY AND SYPHILOLOGY (CANADIAN BRANCH)

D. King Smith, President, 122 Bloor St. West, Toronto.
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Thomas A. Maxwell, Secretary-Treasurer, 1119 Union Indemnity Bldg., New Orleans.

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Lester Hollander, Chairman, Jenkins Arcade Bldg., Pittsburgh.
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Index to Current Literature

DERMATOLOGY

Actinomycosis: Diagnosis and Treatment. T. Eiken, Ugesk. f. Læger **91**:581 (July 11) 1929.

Alcoholic Pseudo Pellagra. E. R. Maloney and L. Tulipan, New York State J. Med. **29**:1063 (Sept. 1) 1929.

Alopecia Areata, with Particular Reference to Etiology. Ronald B. Rogers, J. A. M. A. **93**:919 (Sept. 21) 1929.

Arneth's Neutrophil Picture in Exanthematic Diseases in Relation to Leukocyte Formula. F. Vecchio, Riv. di clin. pediat. **27**:247 (April) 1929.

Articular and Periarticular Complications in Chickenpox. A. Martin, Paris méd. **2**:72 (July 20) 1929.

Burn from High Voltage Current: Case. A. T. Nesbit, Am. J. Roentgenol. **22**:158 (Aug.) 1929.

Butter in Psoriasis. A. B. Grubb, Virginia M. Monthly **56**:330 (Aug.) 1929.

Cancer as Public Health Problem. J. Ewing, Pub. Health Rep. **44**:2093 (Aug. 30) 1929.

Coccidioidal Granuloma: An Epidemiologic Survey, with a Report of Twenty-Four Additional Cases. W. T. Cummins, Joseph J. Smith and C. H. Halliday, J. A. M. A. **93**:1046 (Oct. 5) 1929.

Coccidioidal Granuloma: Report of a Case Treated by Intravenous Dye, Colloidal Lead and Colloidal Copper, with Autopsy Observations. D. Schuyler Pulford and E. Eric Larson, J. A. M. A. **93**:1049 (Oct. 5) 1929.

Control of Impetigo Neonatorum: Advisability of a Radical Departure in Obstetric Care. E. T. Rulison, J. A. M. A. **93**:903 (Sept. 21) 1929.

Cutaneous Respiration in Man: 1. Factors Affecting Rate of Carbon Dioxide Elimination and Oxygen Absorption. L. A. Shaw, A. C. Messer and S. Weiss, Am. J. Physiol. **90**:107 (Sept. 1) 1929.

Dermatitis Caused by Achillea Millefolium. O. Gans, Deutsche med. Wchnschr. **55**:1213 (July 19) 1929.

Detection of Anthrax-Like Bacilli in Impetigo Anthracoides. W. Richter and K. Walther, Deutsche med. Wchnschr. **55**:1089 (June 28) 1929.

Differential Diagnosis and Treatment in Various Forms of Lichen. S. R. Brünauer, Wien. klin. Wchnschr. **42**:942 (July 11) 1929.

Dosage and Technic of Roentgen Therapy in Dermatology. G. H. Schneider, Strahlentherapie **33**:181 (June 29) 1929.

Encephalitis Following Vaccination. A. Eckstein, Klin. Wchnschr. **8**:1153 (June 18) 1929.

Epidermolysis Bullosa: Report of a Case with Lesion Present at Birth. Joseph Garland, J. A. M. A. **93**:918 (Sept. 21) 1929.

Epithelioma of Penis. G. A. Wyeth, Am. J. Surg. **7**:283 (Aug.) 1929.

Erythema Nodosum of Tuberculous Origin. J. Heimbeck, Norsk. Mag. f. Laegevidensk. **90**:566 (June) 1929.

Exfoliative Dermatitis from Potassium Sulphocyanate Therapy. C. R. Weis and Rudolph Ruedemann, J. A. M. A. **93**:988 (Sept. 28) 1929.

General Furunculosis Due to Tetragenous Sarcina, Treated by Autovaccine and Antivirus. B. Galli-Valerio and M. Bornand, Schweiz. med. Wchnschr. **59**:730 (July 13) 1929.

Genesis of Icterus Neonatorum. Editorial, J. A. M. A. **93**:991 (Sept. 28) 1929.

Granuloma Inguinale Resembling Primary Chancre. C. A. Birch, Brit. M. J. **2**:345 (Aug. 24) 1929.

Hemiplegia in Scarlet Fever. J. A. Chavany and P. E. Vannier, Bull. méd. **43**:826 (July 27) 1929.

Herpes Zoster Ophthalmicus Apparently Due to Chronic Frontal Sinusitis. J. E. Landis, Pennsylvania M. J. **32**:765 (Aug.) 1929.

Herpes Zoster Ophthalmicus Treated with Convalescent Serum: Case. J. S. Friedenwald, Bull. Johns Hopkins Hosp. **45**:103 (Aug.) 1929.
Human Sporotrichosis: Case. C. P. Bondurant, South. M. J. **22**:830 (Sept.) 1929.

Infantile Eczema. C. B. Norris, Ohio State M. J. **25**:708 (Sept. 1) 1929.
Infectious Origin of Some Erythemas in Syphilitic Patients Treated with Arsphenamine. G. Garnier, Bull. méd. **43**:829 (July 27) 1929.
Influence of Ultraviolet Rays on Skin Reaction to Tuberculin. L. Storchi, Pediatria **37**:416 (April 15) 1929.

Lesions in Skeletal Muscles in Experimental Scorbutus. G. Dalldorf, J. Exper. Med. **50**:293 (Sept. 1) 1929.

Malignant Pustule with Anthrax Septicemia. Paris, Presse méd. **37**:959 (July 24) 1929.

Negative Tuberculin Skin Reaction in Adults. K. Stetter, Beitr. z. Klin. d. Tuberk. **71**:706 (April 25) 1929.
Neglect of Examination for Hyperalgesia of Skin of Abdomen as Cause of Diagnostic and Therapeutic Errors. I. Boas, Deutsche med. Wchnschr. **55**:1134 (July 5) 1929.

Outbreak of Mild Smallpox in Massachusetts Community. R. P. MacKnight and C. L. Scamman, New England J. M. **201**:361 (Aug. 22) 1929.

Parascarlatina. W. Stern, Monatschr. f. Kinderh. **43**:499 (June) 1929.
Partial Anodontia in Infant with Congenital Syphilis. F. Weiss, Monatschr. f. Kinderh. **43**:507 (June) 1929.
Pathogenesis and Therapy of Psoriasis. E. Pulay, Deutsche med. Wchnschr. **55**:1175 (July 12) 1929.
Pathology of Measles Encephalomyelitis. J. G. Greenfield, Brain **52**:171 (July) 1929.
Pellagra in Wisconsin: Five Cases. M. G. Masten and E. D. Warren, Wisconsin M. J. **28**:419 (Sept.) 1929.
Pemphigus Primary in Larynx. A. B. Murphy, Arch. Otolaryng. **10**:188 (Aug.) 1929.
Percutaneous Immunization Against Diphtheria According to Loewenstein's Method. H. Baar and A. Grabenhofer, Wien. klin. Wchnschr. **42**:930 (July 11) 1929.
Physical Therapy in Skin Ulcers. H. F. Wolf, Am. J. Surg. **7**:239 (Aug.) 1929.
Pruritus Ani: Treatment with Benacol. F. C. Yeomans, R. V. Gorsch and J. L. Mathesheimer, M. J. & Rec. **130**:279 (Sept. 4) 1929.
Psoriasis with Superimposed Bullous Eruption (Pemphigus): Case. D. Bloom, M. J. & Rec. **130**:246 (Sept. 4) 1929.

Relation of Inguinal Lymphogranuloma to Anorectal Syphiloma. A. Koppel, Klin. Wchnschr. **8**:1263 (July 2) 1929.
Relationship of Dermatology to Other Branches of Medicine. H. W. Barber, Lancet **2**:363 (Aug. 24) 1929.
Ringworm of Scalp in Adults: Two Cases. C. White, Illinois M. J. **56**:152 (Aug.) 1929.

Scleroderma: Two Cases. C. C. Harrold, Georgia M. A. J. **18**:354 (Aug.) 1929.
Standard Colors for Use in Study of Vascular Reactions of Human Skin. T. Lewis, Heart **15**:1 (Aug. 3) 1929.
Study of Generalization of Vaccine Virus from Enhanced Skin Lesions. F. W. Stewart and F. Duran-Reynals, J. Exper. Med. **50**:341 (Sept. 1) 1929.
Successive Roentgenograms of Chest of Children During Measles. J. L. Kohn and H. Koiransky, Am. J. Dis. Child. **38**:258 (Aug.) 1929.
Superficial Fungus Dermatitis of Glabrous Skin: 1,024 Cases. C. White, Wisconsin M. J. **28**:341 (Aug.) 1929.

Trambusti's Endodermoreaction to Tuberculin. B. Trambusti, Riv. di. clin. pediat. **27**:241 (April) 1929.
Treatment of Acne Vulgaris with Small Doses of Quartz Lamp Radiation. A. Korsbjerg, Ugesk. f. Læger **91**:568 (July 4) 1929.

Treatment of Acute Eczema with Red and Blue Light. K. Kirschmann, Deutsche med. Wchnschr. **55**:1131 (July 5) 1929.
Tinea of the Toe-Nails as a Source of Reinfection in Tinea of the Feet. Charles Mallory Williams and Else A. Barthel, J. A. M. A. **93**:907 (Sept. 21) 1929.

Use of Silver Foil in Treatment of Wounds. P. Moritsch, Zentralbl. f. Chir. **56**:1410 (June 8) 1929.

Yeast and Pellagra. N. P. Walker, Georgia M. A. J. **18**:379 (Aug.) 1929.

SYPHILOLOGY

Biologic Diagnosis of Congenital Syphilis. F. Lo Presti-Seminerio, Gazz. d. osp. **50**:439 (April 7) 1929.
Biology and Staining of Spirochaeta Pallida. S. Bergel, Klin. Wchnschr. **8**:1218 (June 25) 1929.
Bismuth Arsphenamine Sulphonate: For Intramuscular Use in Syphilis. J. A. Elliott, South. M. J. **22**:785 (Sept.) 1929.

Comparison of Kahn and Wassermann Tests in 684 Mental Patients. F. Proescher and A. S. Arkush, Am. J. Psychiat. **9**:195 (July) 1929.
Comparison of Results by Wassermann and Butler Tests. J. LaZarus, New Orleans M. & S. J. **82**:84 (Aug.) 1929.
Conditions of Immunity in Syphilis. O. Thomsen, Hospitalstid. **72**:586 (May 30) 1929.

Destructive Changes in Shaft of Bones in Nurslings with Congenital Syphilis. B. Epstein and E. Podvinec, Monatschr. f. Kinderh. **43**:397 (June) 1929.
Diagnostic Value of Isolated Pupillary Signs in Cases of Visceral Syphilis. R. A. Luria, Deutsche med. Wchnschr. **55**:1037 (June 21) 1929.

Effect of Heating Syphilitic Serum and Protein Fractions on Precipitation Reaction. M. Nishio, J. Infect. Dis. **45**:148 (Aug.) 1929.

Histologic Changes in Spleen in Early Congenital Syphilis. C. J. Watson, Arch. Path. **8**:224 (Aug.) 1929.

Immune Bodies in Experimental Syphilis. A. Cohn, Klin. Wchnschr. **8**:1310 (July 9) 1929.
Immunity Processes in Syphilis: III. Stock Specific Fixation of Complement and Antibodies. H. Kroó and F. O. Schultze, Klin. Wchnschr. **8**:1203 (June 25) 1929.
Incidence of Syphilis Among Pregnant Negro Women. C. L. Wilson, Am. J. Obst. & Gynec. **18**:215 (Aug.) 1929.
Indications and Contraindications for Treatment of Latent Syphilis. O. Naegeli, Schweiz. med. Wchnschr. **59**:697 (July 6) 1929.
Induced Syphilitic Meningitis (Neurorecurrence). H. J. Morgan, South. M. J. **22**:699 (Aug.) 1929.

Lesions of Latent Syphilis. A. S. Warthin, Brit. M. J. **2**:236 (Aug. 10) 1929.

Malaria Therapy of Paresis. J. Lépine, L. Bourrat, H. Christy and E. Larrivé, J. de méd. de Lyon **10**:397 (June 20) 1929.

Present Status of Clinical Aspects of Syphilis of Stomach. H. Schlesinger, Wien. klin. Wchnschr. **42**:861 (June 27) 1929.
Prevention of Syphilis in Virginia. C. B. Ransone, Virginia M. Monthly **56**:307 (Aug.) 1929.
Progress in Syphilis, 1928. A. W. Cheever, New England J. M. **201**:369 (Aug. 22) 1929.

Relation of Syphilis and Yaws. C. S. Butler, Ann. Int. Med. **3**:175 (Aug.) 1929.

Syphilis in Which Death Followed After Administration of Sulpharsphenamine: Case. J. R. Williams and H. E. Pfluke, New York State J. Med. **29**:1071 (Sept. 1) 1929.
Syphilis of Heart and Aorta. J. Cowan and J. S. Faulds, Brit. M. J. **2**:285 (Aug. 17) 1929.

Syphilis of Stomach: Case. J. A. Johnson, Minnesota Med. **12**:496 (Aug.) 1929.
Syphilitic Amenorrhea. Milian and Perin, Bull. et mém. Soc. méd. d. hôp. de Paris **53**: 736 (June 17) 1929.

Value of Guttadiaphot Method in Diagnosis of Syphilis. V. Schilling, Med. Klin. **25**:1022 (June 28) 1929.

Wassermann Reaction of Human Milk: 107 Cases. J. Jarcho, J. Lab. & Clin. Med. **14**:1097 (Aug.) 1929.

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